Health Economics in Osteoporosis: Construction and Application of a New State-Transition Microsimulation Model

By

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Declaration of originality

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Statement of co-authorship

This thesis includes papers for which Lei Si (LS) is first but not sole author. LS led the work in developing and conceptualising the papers, implementing the analyses and writing the manuscripts under the primary supervision of Andrew Palmer (AP) and co-supervisor Tania Winzenberg (TW). Throughout the work presented herein he was assisted by co-authors from both domestic and international alliances. Detailed below are the contributions of LS and each of his co-authors for each respective paper.

1. The paper reported in Chapter 2:

Si L, Winzenberg TM, Palmer AJ. A systematic review of models used in cost-effectiveness analyses of preventing osteoporotic fractures. *Osteoporosis International*, Jan 2014; 25(1): 50-60.

- LS developed the review protocol following the PRISMA Statement. LS developed the search strategy in different databases. The search strategy was reviewed by TW and AP. LS performed the data collection, extraction and statistical analysis. The analysis was conducted under the supervision of AP and TW. LS drafted the manuscript and coordinated revisions and submission.
- AP was involved in the initial development, and reviewed the extraction of data. AP assisted in the interpretation of the results and assisted with manuscript revisions.
- TW was involved in conceptualising the paper, helped with interpretation of the results and assisted with manuscript revisions.

2. The paper reported in Chapter 3:

Si, L., Winzenberg TM, de Graaff B and A.J. Palmer, A systematic review and meta-analysis of utility-based quality of life for osteoporosis-related conditions. *Osteoporosis International*, Aug 2014, 25(8): 1987-97.

- LS developed the review protocol following the PRISMA Statement. LS developed the search strategy in different databases. The search strategy was reviewed by TW and AP. LS performed the data extraction and statistical analysis. The analysis was conducted under the supervision of AP and TW. LS drafted the manuscript and coordinated revisions and submission.
- AP was involved in the initial development, and reviewed the extraction of data. AP assisted in the interpretation of the results and assisted with manuscript revisions.
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3. The paper reported in Chapter 4:

Si L, Winzenberg TM, Jiang Q, Palmer AJ. Screening for and treatment of osteoporosis: construction and validation of a state-transition microsimulation cost-effectiveness model. *Osteoporosis international*, May 2015. 26(5): 1477-89.

- LS conceptualised the paper, built the health economics model and wrote the manuscript. LS tested the model face validity, internal validity and external validity. LS conducted base-case analysis, one-way and probabilistic sensitivity analyses. LS coordinated revisions and submission.
- TW assisted in the process of model face validation, analysis interpretation and manuscript revisions.
- QJ assisted in acquisition of model parameter values and assisted in performing the analyses.
- AP assisted in the model construction, result interpretation and manuscript revisions.

4. The paper reported in Chapter 5:

Si L, Winzenberg TM, Chen M, Jiang Q, Palmer AJ. Residual lifetime and 10-year absolute risks of osteoporotic fractures in Chinese men and women. *Current Medical Research & Opinion*, June 2015. 31(6):1149-56.

- LS developed the analysis plan, conceptualised the paper, conducted the statistical analyses, wrote the manuscript and coordinated revisions and submission.
- TW reviewed the manuscript and assisted in results explanation. TW assisted in manuscript revision.
- MC and QJ assisted in acquisition of model parameter values. QJ assisted in liaison with clinicians on data explanations.
- AP assisted with the conceptual analysis plan, assisted in the cost-of-illness analysis and helped revise the manuscript.

5. The paper reported in Chapter 6:

Si L, Winzenberg TM, Jiang Q, Chen M, Palmer AJ. Projection of Osteoporosis-Related Fractures and Costs in China: 2010-2050. *Osteoporosis International*, July 2015. 26(7): 1929-37.

- LS developed the research plan, conceptualised the paper, conducted the

statistical analyses, wrote the manuscript and coordinated revisions and submission.

- TW reviewed the manuscript and assisted in manuscript revision.
- MC and QJ assisted in acquisition of model parameter values. MC assisted in data explanation.
- AP assisted with the conceptual analysis plan, assisted in the statistical analysis and helped revise the manuscript.

6. The paper reported in Chapter 7:

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- LS developed the analysis plan, conceptualised the paper, conducted the health economics analyses, wrote the manuscript and coordinated submission.
- TW assisted in inclusion of different osteoporosis screening techniques. TW reviewed the manuscript and assisted in results explanation.
- MC and QJ assisted in acquisition of model parameter values. QJ assisted in liaison with clinicians on information of current osteoporosis management in China.
- TW, MC, QJ, AM and AP reviewed the manuscript.
- AP assisted with the conceptual analysis plan, assisted in the cost-effectiveness analysis and helped revise the manuscript.

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Abstract

Osteoporosis is a chronic disease causing a huge disease and economic burden to the society. Many screening and treatment interventions are effective at preventing osteoporotic fractures, while implementation of such interventions incur substantial costs. Health economics modelling plays a critical role in evaluations that aim at identifying interventions representing the best value for money. This thesis presents the construction and validation of a new state of the art osteoporosis health economics model, and key important examples of its application in the health economic evaluation of screening for osteoporosis and fracture prevention.

Chapter 1 presents a general introduction to osteoporosis and health economics.

Chapter 2 presents a systematic review of all osteoporosis health economic models and the evolution of modelling in the field of osteoporosis over the past decades. Osteoporosis health economic models have improved with the development of more sophisticated modelling techniques. In addition, medication persistence and adherence have become increasingly recognized as important factors influencing the long-term cost-effectiveness of osteoporosis treatments and have been increasingly incorporated in recent models. This review then guided the development of a state of the art model that built on the strengths and overcame the deficiencies identified.

One of the key issues in the cost-effectiveness analysis is to assign the health related-utility values (HSUVs) to different disease states. Chapter 3 presents the development of a standard set of HSUVs for osteoporosis-related conditions using a systematic review and meta-analysis approach. Fracture events have great impacts on HSUVs, particularly for patients with hip and clinical vertebral fractures, but multiple studies have produced a range of values for the impact of fractures on HSUVs. A systematic review and meta-analysis is performed in order to provide summary measures of HSUVs before and after fractures, to be used in future health economics models. HSUVs improve with time after fracture events, but still remain lower when compared with pre-fracture HSUVs.

Chapter 4 is the key to this thesis, and documents the development and validation of a new state of the art osteoporosis health economics model. The model is a state-transition microsimulation model incorporating major clinical outcomes of osteoporosis. It is validated in the Chinese population but is flexible to be adapted to other populations, and demonstrates

good face, internal and external validities.

Chapter 5 to 7 are three key examples of the model application in cost-of-illness and cost-effectiveness studies. Chapter 5 presents the first example of the application of the new osteoporosis health economics model to estimate the absolute risks of osteoporotic fractures in the Chinese population. More than 40% of Chinese women and approximately 10% of Chinese men aged 50 years are expected to have the first osteoporotic fracture in their remaining lifetimes. Compared to the rest of the world, Chinese women have higher age-matched risks of osteoporotic fractures.

Chapter 6 presents the second example of the model's application: a cost-of-illness study, which quantifies the magnitude of the cost of osteoporosis fractures in China. Annual fracture numbers and costs are estimated for the entire Chinese population. Additionally, projections of the number and costs of fractures through to the year of 2050 are performed. Approximately 2.33 (95% CI: 2.08, 2.58) million osteoporotic fractures are estimated to occur in 2010, costing USD 9.45 (95% CI: 8.78, 10.11) billion. The number and costs of fracture are estimated to double by 2035 if no action is taken.

Chapter 7 presents the third example of the model's application. While Chapter 6 informs us of the size of the problem, Chapter 7 identifies possible strategies to address the problem. A cost-effectiveness analysis of different osteoporosis screening and treatment strategies is conducted using the osteoporosis health economics model. Pre-screening with quantitative ultrasound (QUS) with subsequent dual energy X-ray absorptiometry (DXA) screening if the QUS T-score$\leqslant$-0.5 with a 2-year rescreening interval in the Chinese women starting at age 55 is the most cost-effective. Moreover, screening and treatment strategies are cost saving if the screening initiation age is 65 years.

This thesis presents a range of health economic modelling studies with its construction, validation and application in health economic evaluations. This work will be useful in the scientific community and healthcare decision making in osteoporosis. Further, the model will be adapted to other populations to support the pharmaceutical submissions and identifications of osteoporotic fracture preventions that present best value for money.

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Chapter 1: General introduction and outline

1.1 Introduction of osteoporosis

The word osteoporosis comes from the Greek term for "porous bones", where "osteo" is for bones and "porosis" denotes porous. Osteoporosis is characterised by low bone mineral density (BMD) and micro-architectural deterioration of bone tissue [1]. Patients with osteoporosis have increased risks of fracture. While the definition of osteoporosis takes both density and quality of bone into account, bone quality is hard to measure in clinical practice. A number of factors contribute to bone quality such as bone turnover, geometry, components of the bone minerals and micro-architecture [2]. The diagnosis of osteoporosis is, therefore focused on bone density [3].

1.1.1 Diagnosis of osteoporosis

Threshold values are critical in the diagnosis of osteoporosis, where thresholds denote cut-off values for BMD. The threshold value is the number of standard deviations (SDs) of the BMD measurement above or below that of the reference population [3]. When the reference is the young adult population, the threshold value is called a T-score. Alternatively, when the population of the same ages is used as the reference, the threshold value is called a Z-score. The reason for using the difference in SDs of BMD rather than the actual values arose from the distribution of the BMD in young healthy adults: BMD was found to remain constant until about age 50 years, and it fitted a normalised Gaussian distribution [3, 4]. The criteria for the diagnosis of osteoporosis in women by the World Health Organisation was suggested as "*hip BMD by dual energy X-ray absorptiometry (DXA) 2.5 SD or more below the young adult female mean, i.e. T-score≤-2.5*" [2, 3, 5]. It was acknowledged that suitable diagnostic BMD threshold values in men were less well defined compared with that in women, "*a similar cutoff value for hip BMD that is used in women can be used in the diagnosis of osteoporosis in men-namely, a value for BMD 2.5 SDs or more below the average for women*" [3, 6].

In addition to the diagnostic criteria for osteoporosis, three other categories of osteoporosis-related conditions had been proposed by the WHO and revised by the International Osteoporosis Foundation (IOF) [2, 3, 5].

- **Normal:** hip BMD greater than 1 SD below the young adult reference mean (T score ≤–1).
- **Low bone mass (osteopenia):** hip BMD greater than 1 SD below the young adult mean, but less than 2.5 SD below this value (T score < –1 and > –2·5).
- **Severe osteoporosis (established osteoporosis):** hip BMD 2.5 SDs or more below the young adult mean in the presence of one or more fragility fractures.

BMD measured at the hip is used in the diagnosis criteria of osteoporosis, because hip BMD is the most precise predictor of a hip fracture which is the most severe complication of osteoporosis in terms of mortality increase and quality-of-life (QoL) reduction [7, 8]. BMDs measured at other sites are also critical in terms of fracture risk assessment rather than diagnosis.

1.1.2 Prevalence of osteoporosis

As osteoporosis is defined based on BMD levels, given ethnic differences in BMD [9], it is not surprising to observe different prevalence rates of osteoporosis worldwide. In an American study comprised 197,848 postmenopausal women from five ethnic groups, Black women had the highest BMD, followed by Caucasians and Asians. Based on WHO criteria of diagnosing osteoporosis, 4.2%, 7.2% and 10% of Black, Caucasian and Asian women were osteoporotic [9]. In Europe, more than 27.6 million people were estimated to live with osteoporosis in 2010 [10]. Compared with American women, the prevalence of osteoporosis in a European Caucasian population was more than twice as high: the prevalence of osteoporosis in Swedish women aged 50-84 years was 21% [10]. Prevalence of osteoporosis in Australian women was estimated at 23% which was close to that in European women [11]. In Chinese women aged over 50 years, the prevalence of osteoporosis was estimated at 12.5% which was relatively low compared with the Caucasian population [12]. Irrespective of ethnic groups, prevalence rates of osteoporosis were 2-4 times those in men [9-12]. Generally, prevalence rates of osteoporosis detected by BMD scan are higher than the self-reported estimates [11]. It reflects the fact that osteoporosis is still underdiagnosed due to the absence of overt symptoms [13].

1.1.3 Fractures and osteoporosis

Patients with osteoporosis have higher risks of fractures [14-17] and fractures can occur at various sites in the skeletal system. The most common osteoporotic fractures occur at the hip, vertebrae and distal forearm (wrist) [18].

Osteoporotic hip fractures are typically caused by a fall or low energy trauma, such as bumping into a sharp corner. Femoral neck fractures and intertrochanteric hip fractures are the most common hip fractures (*Figure 1.1*) [19]. Femoral neck fractures occur in the narrow section of the bone between the main shaft of the femur and the ball, while intertrochanteric hip fractures occur just below the femoral neck. Hip fractures might also occur at the shaft of the femur, i.e. subtrochanteric fractures, but they are less common.

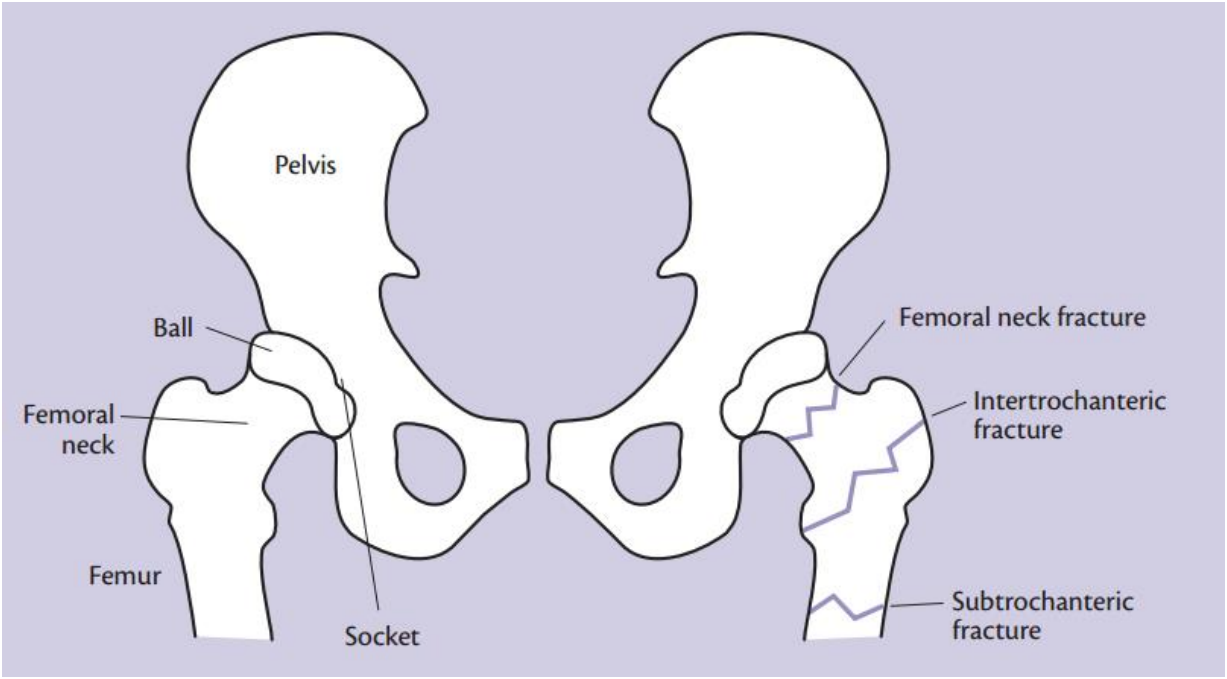

Figure 1.1 Bones of the hip and sites of hip fractures. Source: AIHW (2008) Arthritis and osteoporosis in Australia 2008. Arthritis series no 8 Cat no PHE 106 AIHW, Canberra [19].

Vertebral fractures related to osteoporosis also commonly lead to bone deformities. The vertebral column consists 33 vertebrae [20], they are stacked and are separated from each other by intervertebral discs. There are three types of vertebral compression fractures: wedge fractures, biconcave fractures and crush fractures. The most common vertebral fractures are wedge fractures [21]. The vertebrae form a wedge shape but do not move out of place and the spinal cord is rarely affected in wedge fractures, patients with a number of wedge fractures often present a hunched posture and a reduced height [22-25]. Biconcave fractures refer to collapse of the central portion of both vertebral body endplates (*Figure 1.2*) [26]. While crush fractures refer to collapse of entire vertebral body. Approximately three in four patients with compression fractures remain asymptomatic, they normally remain underdiagnosed and undertreated until more severe clinical consequences occur [27, 28].

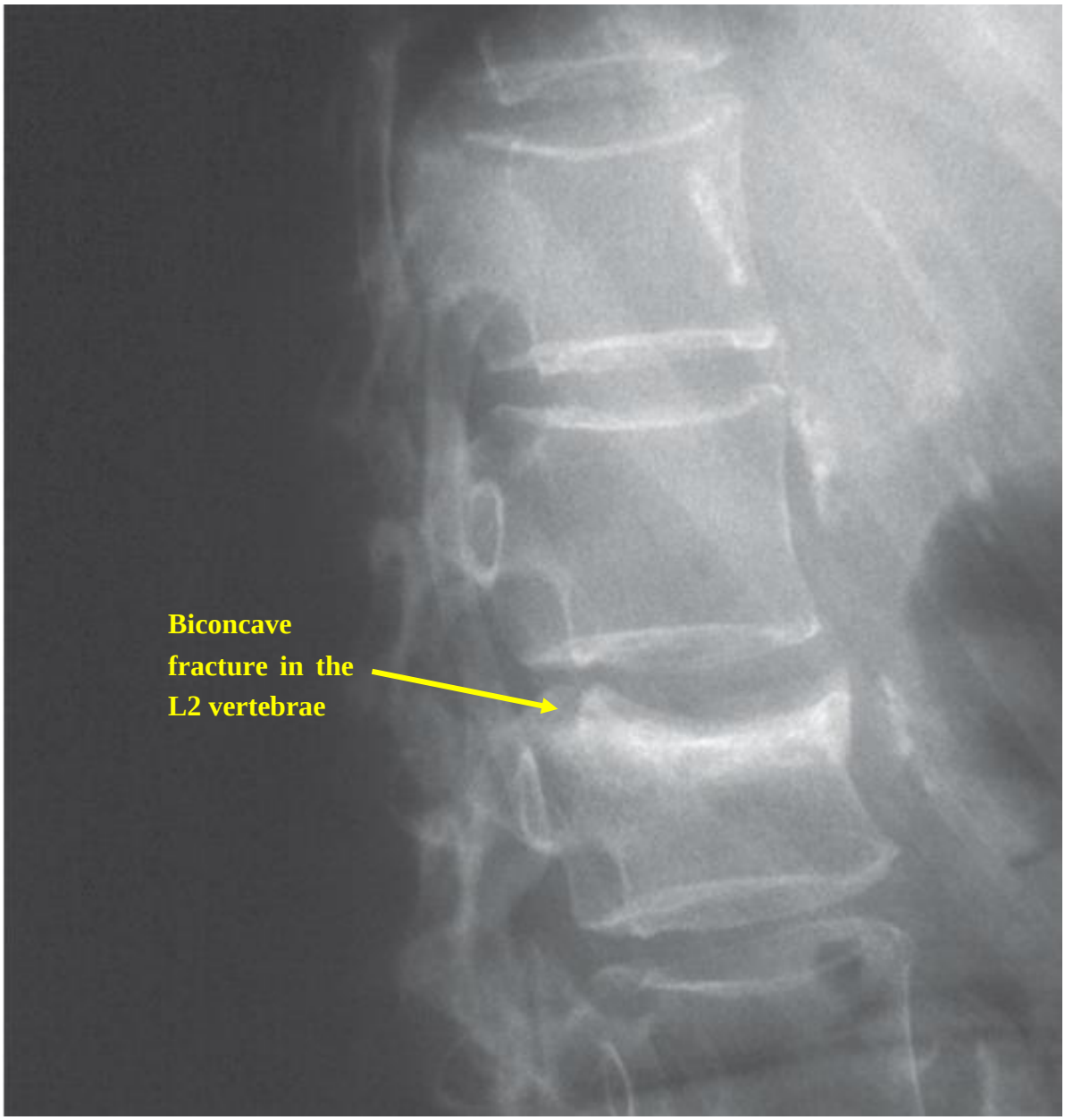

Figure 1.2 Lateral radiograph of the spine and a biconcave fracture in the L2 vertebrae. Source: Ensrud KE, Schousboe JT (2011) Vertebral Fractures. New England Journal of Medicine 364:1634-1642.

Wrist fractures often occur when patients with osteoporosis fall on a hard surface, the most common wrist fracture is called Colles' fracture which occurs at the lower end of the radius (*Figure 1.3*). In addition to fractures at hip, vertebrae and wrist, fractures can occur at any bones that are weight bearing (such as pelvis and ankle), or stress taking when the patients fall (such as forearms, upper arms and shoulder) [19, 29, 30].

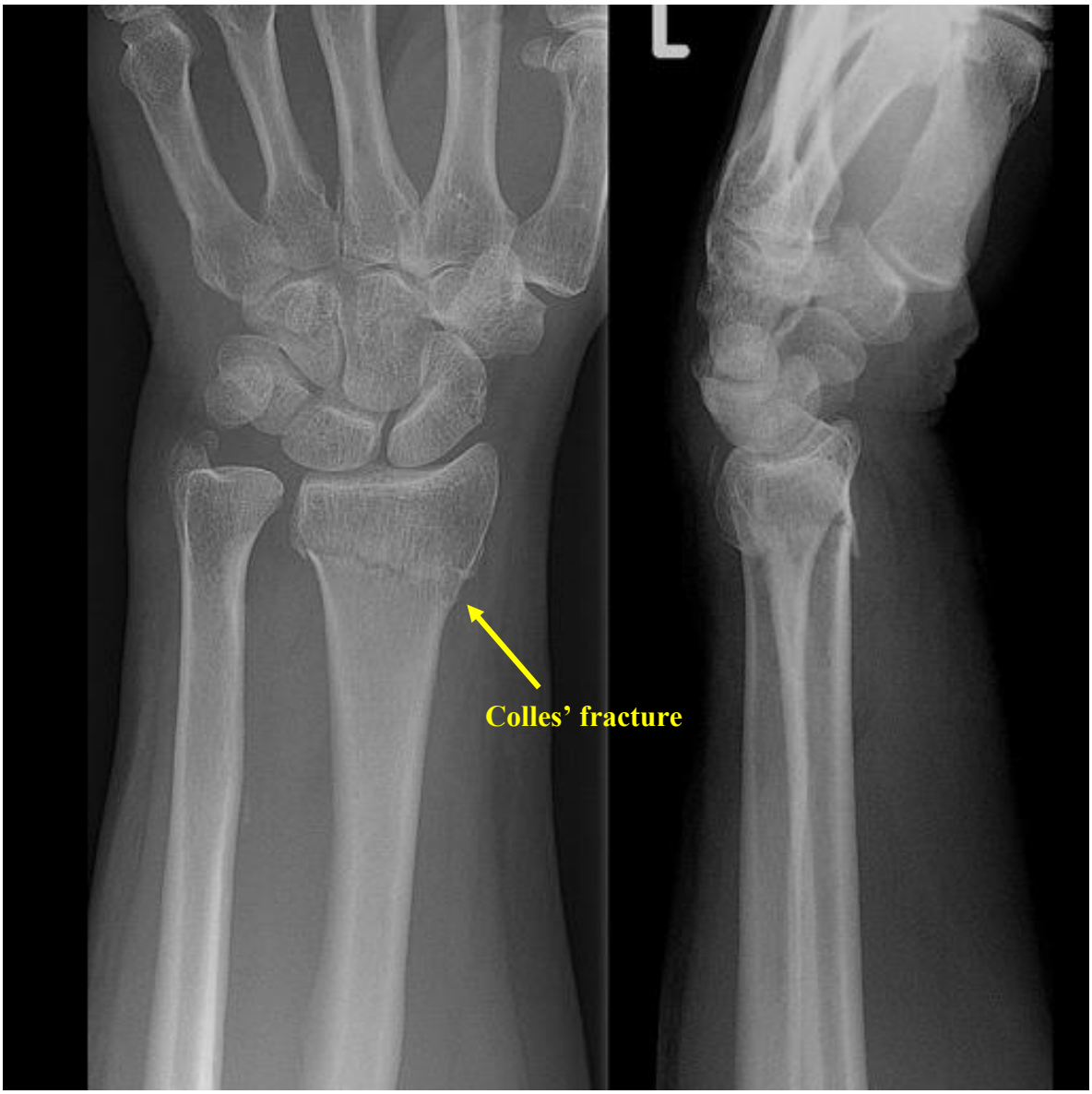

Figure 1.3 Colles' fracture on X-ray.

Source: https://commons.wikimedia.org/wiki/File:Collesfracture.jpg [31]

1.1.4 Clinical risk factors for osteoporosis and osteoporotic fractures

Numerous clinical risk factors (CRFs) have been identified for osteoporosis and osteoporotic fractures including: low BMD [32], female sex [33], premature menopause [34], age [35], increased rate of falls [36], primary or secondary amenorrhoea [37], primary and secondary hypogonadism in males [38], Asian or white ethnicities [33, 39], previous osteoporotic fractures [40, 41], glucocorticoid use [42], high bone turnover [43], family history of osteoporosis or osteoporotic fractures [40, 44], low body-mass index (BMI) [45, 46], neuromuscular disorders [47], smoking [48, 49], excessive alcohol consumption [50], low dietary calcium intake [51, 52] and vitamin D deficiency [48].

T-score derived from BMD is a critical indicator used in the definition of osteoporosis. Low BMD was found to be associated with higher fracture risks, with a 2- to 3-fold increase in fracture incidence for one SD reduction in BMD [32]. However, assessment of osteoporotic fracture risk should not solely based on BMD, as other CRFs such as older age, smoking and family history of fracture were found to increase with fracture risks independent of BMD [44, 49, 53].

1.1.5 Assessment of fracture risk

As CRFs play an important role in the assessment of fracture risk, they have been incorporated in many widely used individualised fracture risk assessment tools, rather than the use of BMD alone, for a more precise estimation of future fracture risk. For example, the FRAX® tool which has been developed by the WHO incorporated 10 CRFs (age, sex, BMI, previous fracture, parent hip fracture, smoking, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis and excessive alcohol consumption) with or without BMD results [54]. The Garvan Fracture Risk Calculator has incorporated 4 CRFs (history of prior fracture, history of fall during the past 12 months, age and BMD) [55].

The overall accuracy of different risk assessment tools is satisfactory [56]. The 10-year or 5-year fracture risks assessed from the risk assessment tools may help inform clinicians to decide whether or not their patients should receive treatment to prevent future fractures.

1.1.6 Clinical consequences of osteoporotic fractures

Patients with an osteoporotic fracture have a higher risk of subsequent fractures [7, 57], increased risk of mortality [7] and loss of QoL [58].

The Dubbo Osteoporosis Epidemiology Study has shown that the relative risk (RR) of subsequent fractures was generally more than 2-fold independent of BMD levels: the RR of subsequent fractures ranged from 2.0 (95% confidence interval, CI: 1.2, 3.3) for women with normal BMD to 3.2 (95% CI: 2.7, 3.9) for those with diagnosed osteoporosis [7]. The RR of subsequent fractures highly dependent on the site of previous fracture: the RR after a hip fracture was 9.97 (95% CI: 1.38, 71.98), and that following a clinical vertebral fracture was as high as 15.12 (95% CI: 6.06, 37.69) in younger men [57]. Moreover, the Dubbo study has demonstrated higher RR of mortality, particularly in those with low BMD: the standardised mortality ratio was 1.3 (95% CI: 1.1, 1.7) for women with osteopenia and 1.7 (95% CI: 1.5, 2.0) for women with osteoporosis [5].

Quality of life is the general wellbeing and health of individuals across physical, mental and social aspects. Health related health utility values (HSUVs) are cardinal values that represent the patients' preferences on health [59]. In a recent meta-analysis on HSUVs for osteoporosis-related conditions, patients with osteoporotic fractures were shown to have lower HSUVs compared with pre-fracture condition: a 25%, 22% and 5% deduction of HSUVs were found for a hip, clinical vertebral and wrist fracture respectively [8]. Time after fracture was associated with the change of HSUVs: HSUVs declined immediately after a fracture, but improve with time [8, 58, 60].

1.1.7 Osteoporotic fracture prevention

Osteoporotic fracture prevention can be categorised into primary and secondary prevention, where primary prevention targets high risk population of osteoporotic fractures and secondary prevention refers to prevention strategies for those who have had osteoporotic fractures.

To date, there are a number of pharmaceuticals available to prevent fractures. According to different mechanisms in the bone remodelling cycle, osteoporosis drugs can be categorised into either antiresorptive medications or anabolic medications. Antiresorptive medications slow the bone loss, and include bisphosphonates, calcitonin, denosumab, estrogen and estrogen agonists. Anabolic medications increase the rate of bone formation such as teriparatide. Clinical efficacies of osteoporosis medications varied in primary and secondary prevention, in addition, clinical efficacies were different in fracture sites. For example, alendronate was shown to be both effective in the primary and secondary prevention of vertebral fractures with both RR reductions of 45% in postmenopausal women. However, it was only effective in the secondary prevention of non-vertebral fractures with a RR reduction of 22% [61].

In addition to medication treatments, addressing other clinical factors is also important. For example, patients with osteoporosis are encouraged to exercise especially some weight-bearing activities to improve the balance and muscle strength and ultimately prevent falls [62]. Good nutrition and dietary supplements of calcium and vitamin D is also beneficial in osteoporotic fracture prevention [63]. In addition, patients with osteoporosis or osteoporotic fractures should quit smoking and limit alcohol consumption. In case of a fall, hip protectors have been shown to be effective in preventing hip fractures [64].

1.2 Introduction to health economics

1.2.1 Definition of health economics

In 1963, Kenneth Arrow published an article entitled "Uncertainty and the welfare economics of medical care" in *The American Economic Review* [65]. This paper has been recognised as not only one of the most cited articles in health economics, but also as a creation of this discipline [66]. In Arrow's paper, he has identified factors that distinguished health from other goods including extensive government interventions, intractable uncertainties, asymmetric information, barriers to entry, externalities and the presence of a third party agent [67]. These factors make health economics unique to classic economics, however, the scarcity of resources is the common factor in all sub-disciplines of economics and health economics is no exception. The World Bank has defined health economics as

> *"the study of how scarce resources are allocated among alternative uses for the care of sickness and the promotion, maintenance and improvement of health, including the study of how healthcare and health-related services, their costs and benefits, and health itself are distributed among individuals and groups in society."*

In summary, it is a study of allocation of scarce healthcare resources. There are generally two issues that should be considered: efficiency and equity. Efficiency is satisfied when the allocation of scarce resources maximises the achievement of aims [68], i.e. the best use of scarce resources. The concept of efficiency is derived from Pareto efficiency which describes a state of allocation of resources in which it is not possible to make any individual better off without making other individuals worse off [69]. There are three types of efficiencies: technical, economic and social efficiency.

Technical efficiency is a concept that is used in considering how outputs, e.g. health, are produced from inputs, e.g. healthcare resources [70]. Technical efficiency is achieved when the most number of outputs are produced with the least number of inputs. Rather than using the number of inputs to evaluate technical efficiency, economic efficiency is interested in the costs of inputs. Economic efficiency is achieved when the most outputs are produced with the least/given costs [70]. Social efficiency is a much broader concept compared with the first two efficiencies, it is the same as the Pareto efficiency in which both the utilities of suppliers and consumers are achieved [70].

Different from the concept of efficiency, equity is "the absence of avoidable or remediable

differences among groups of people, whether those groups are defined socially, economically, demographically, or geographically [71].” Equity is closely attached to the concepts of needs and social justice, in the egalitarian theory, equity is achieved when everybody in the society have the same opportunities to obtain benefits even if the outcomes are different [72]. However, in the utilitarian theory, equity equals to equality where equal benefits are distributed across the population [70]. In health, we should differentiate equity from equality because health is a fundamental human right.

In this thesis, we focus on the issue of efficiently allocate scarce healthcare resources in osteoporosis. The explicit criteria for making choices in resource allocation is economic evaluation.

1.2.2 Health economic evaluation

Economic evaluation can be defined as the comparative analysis of alternative courses of action in terms of both their costs and consequences [73]. There are different types of health economic evaluations according to the type of comparison of the costs and consequences: cost-minimisation analysis (CMA), cost-benefit analysis (CBA), cost-effectiveness analysis (CEA) and cost-utility analysis (CUA).

There were debates around whether to include CMA as a form of economic evaluation, however, it is still used in the pharmaceutical submissions in some countries including Australia [74]. The premise of CMA is that the effectiveness or efficacies across different interventions should be identical, then cheapest intervention is the choice of interest. In CMA, the fact of equivalent outcomes in different interventions must be presented transparently and comprehensibly. CMA was recommended for economic evaluations in Drummond *et al.* (1997 edition) because of its simplicity and ease of analysis and interpretations [75]. However, Briggs and O’Brien declared the “*death of CMA*” in 2001 [76] and in 2013 Dakin and Wordsworth suggested “*CMA is not only dead but should also be buried*” [77], and Drummond *et al.* have no longer considered CMA as a form of full economic evaluation and regarded it as inappropriate in most situations [73]. The reasons for excluding CMA include, first, the parameter uncertainties fail to be fully addressed in CMA [76]; second, quality-adjusted life years may differ between treatment in after-trial period even if equivalence is demonstrated in the clinical trial period [76]. Nevertheless, continued use of CMA within a trial-based economic evaluation is still acceptable only in trials with non-inferiority or equivalence outcomes [77].

CBA assesses whether the benefits in the monetary value of an intervention outstrip its costs

using measures such as the benefit-cost ratio (BCR) and net present value (NPV) [78]. The BCR calculates the ratio of discounted total benefits and discounted total costs:

$$\text{BCR} = \frac{PV_{benefits}}{PV_{costs}}$$

where $PV_{benefit}$ denotes the present value of benefits and PV_{costs} denotes the present value of costs.

NPV is the difference between discounted benefits and discounted costs as they occur over time:

$$\text{NVP} = \sum_{t=0}^{n} \frac{(Benefits - Costs)_t}{(1+r)^t}$$

where r denotes the discount rate, t represents the year and n denotes the analytic horizon.

A program with a positive NPV or a BCR greater than one indicates the benefits exceed its costs and implementing this program will generate a net benefit to society. As CBA incorporates benefits in monetary terms, it is useful in economic evaluations not only within the healthcare sector but across other sectors in the economy [73].

However, placing a monetary value to human life creates challenges to social justice and methods in calculating the cost of life. Alternatively, CEA and CUA measure the benefits of the intervention in health units and therefore have been extensively used the health sector [79]. CUA measures health outcomes in generic terms, such as quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs), to allow comparisons between health interventions in different disease fields, it is a special form of CEA. The terms of CUA and CBA are often interchangeably used in health economic evaluation studies, we will use CEA as a generic term for both CEA and CUA to avoid confusions [73].

In CEA, two interventions are compared by the incremental cost-effectiveness ratio (ICER) which is calculated by the difference in costs divided by the difference in their effectiveness. ICER represents the incremental costs associated with one additional unit of measure of effectiveness gained. The effectiveness is measure by natural units such as fractures averted, change in systolic or diastolic blood pressure, deaths prevented, adverse events averted and so on. When ICER is calculated, it is compared with a ceiling ratio, λ, to evaluate whether the intervention is cost-effective. The ceiling ratio is called willingness-to-pay (WTP) threshold. An important way to visualise the possible results of ICER is called “cost-effectiveness plane”

which was developed by Black in 1990 [80].

1.2.3 Cost-effectiveness plane

Cost-effectiveness plane is a two-dimensional space where the x axis represents the difference in effectiveness and y axis represents the difference in costs, the comparator is placed at the origin and an intervention of interest can be placed anywhere in the cost-effectiveness plane based on its incremental costs and effectiveness compared with the comparator. The cost-effectiveness plane is given in *Figure 1.2*.

If an intervention has a higher effectiveness and lower costs, it is placed in the south-east quadrant. The intervention dominates the comparator and it is cost-saving. On the contrary, if the intervention is more costly but has lower effectiveness compared with the comparator, it is placed in the north-west quadrant. In this case, it is dominated by the comparator and should not be considered as cost-effective. In most cases, the intervention is placed in the north-east quadrant which means it is more costly but also creates more effectiveness compared with the comparator. In this case, there is a trade-off between the costs and effectiveness: whether or not this intervention is cost-effective depends on a willingness-to-pay (WTP) ceiling for an additional effectiveness gained. This ceiling is called WTP threshold [81], it is illustrated as the solid red line in *Figure 1.2*. If the intervention is placed under the WTP threshold, it is considered cost-effective. Similar theory can be applied to interventions in the south-west quadrant, in which interventions create lower effectiveness but also incur lower costs. The trade-off in this quadrant refers to the saving on costs and effectiveness forgone, similarly, interventions below the WTP threshold are considered as cost-effective.

WTP thresholds vary in countries. In the UK, a range between £20,000 to £30,000 per QALY gained has been used by the National Institute for Health and Care Excellence (NICE) [82], although a recent study suggested this widely used threshold may be too high [83]. In the US, the threshold of US$50,000 per QALY gained is often used in the cost-effectiveness studies [84]. In Australia, the Australian Pharmaceutical Benefit Advisory Committee was unlikely to recommend a drug for listing on the Pharmaceutical Benefit Scheme if the ICER is higher than AU$76,000 [85]. For countries that do not have a predetermined WTP threshold, the WHO recommended 1 to 3 times per capita gross domestic product (GDP) as the WTP threshold and this recommendation was used in China [86, 87].

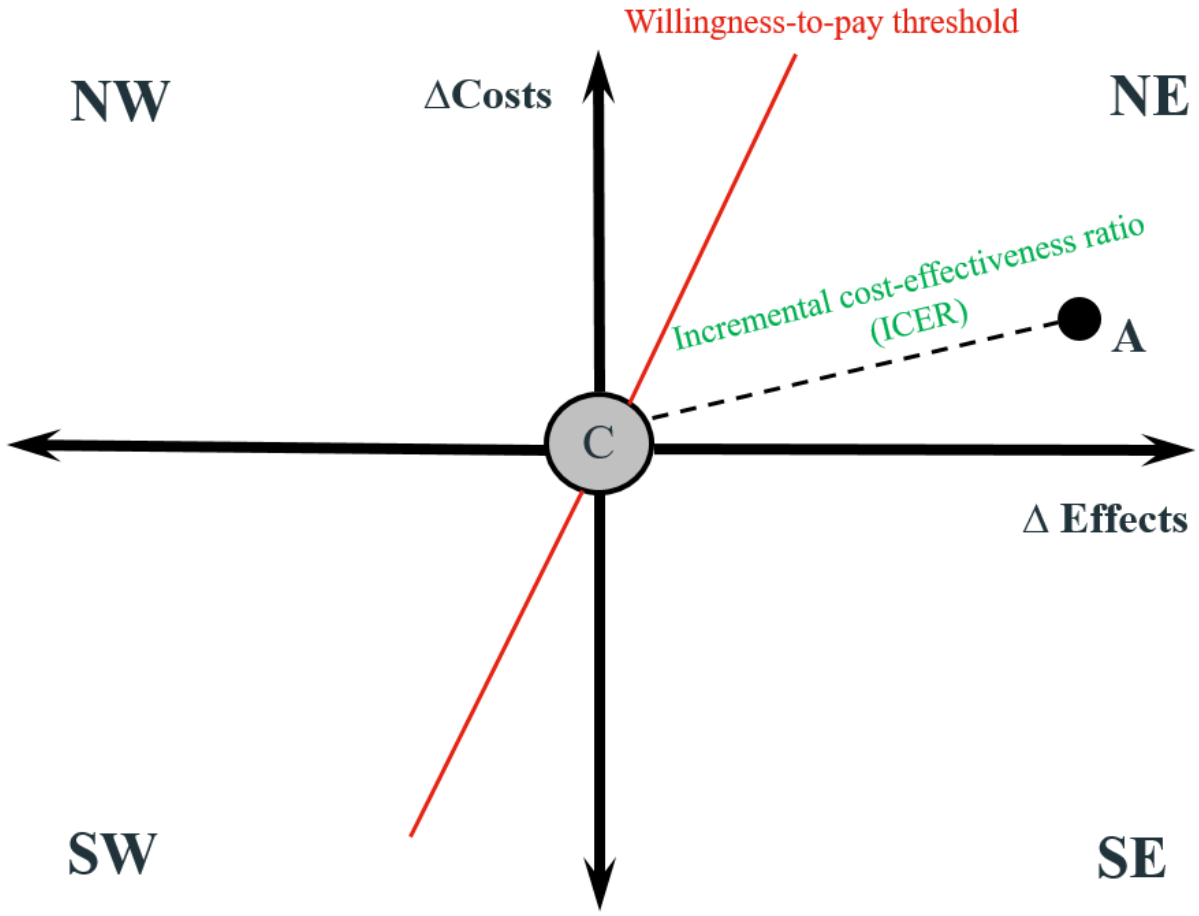

Figure 1.2. The cost-effectiveness plane, adapted from Black 1990 [80]. Given the difference in costs and effectiveness compared to the comparator (C), the new intervention (A) can be placed in any of the four quadrants in the cost-effectiveness plane: the north-east (NE), south-east (SE), south-west (SW) and north-west (NW). The slope of the line between A and C (dotted line) denotes the difference in costs over the difference in effects, i.e. the incremental cost-effectiveness ratio (ICER). The solid red line denotes the willingness-to-pay (WTP) threshold which demonstrates the maximum acceptable value to be paid for one unit of additional effects gained.

1.2.4 Methods of conducting a health economic evaluation

Generally, a health economic evaluation can be undertaken alongside a clinical trial or through economic modelling. Clinical trials have been recognized as the best vehicle for economic evaluations, because trials are able to provide the best interval validity [88]. In addition, economic evaluation alongside trials enables economists analyse individual-level data using statistical and econometric techniques at an early opportunity [73, 89]. Furthermore, the collection of economic data only adds modest marginal cost to the clinical trials where large

proportion of the trial budget are spent on collecting clinical data [30].

While there are several advantages of conducting a health economic evaluation alongside clinical trials, health economic evaluations solely based on data collected from clinical trials are rare due to the following reasons.

First, the rationale of choosing included therapies is different from the clinical trial and economic evaluation perspective. Clinical trials are the most rigorous way to determine the causal relationship between treatment and outcome, the treatment included in the intervention group is a new treatment of interest and the placebo group is the comparator [90]. In economic evaluation study, the choice of included therapies should depend on whether the new treatment is intended as an adjunctive therapy or as a substitute for an existing treatment [73]. In addition, there are normally more than one interventions included in an economic evaluation while in clinical trials the intervention group normally incorporate only one therapy [91].

Second, health economic evaluations normally require numbers of parameters that might not be fully captured in a single clinical trial [81]. Furthermore, clinical effectiveness of an intervention shown in the real world might differ from clinical efficacy from trials [92]. In a trial, clinical efficacy is generated under ideal circumstances with strict inclusion criteria of study population including patient characteristics, conditions under investigation, drug regimens and co-morbidities. However, effectiveness research takes into account patient-, provider-, and system-level factors that may affect an intervention's effectiveness [93]. In the context of economic evaluation studies, where the interventions are given to the communities, effectiveness research can be more relevant to healthcare decision making.

Finally, some clinical trials use surrogate endpoints and the duration of the trials might not enough to capture all relevant outcomes of the intervention [94]. However, economic evaluations including cost-effectiveness analysis use clinically meaningful endpoints such as mortality, which might not be captured in the short duration of clinical trials. Furthermore, evidence has shown a legacy effect even after the cessation of clinical trials [95].

In summary, a well-designed health economic evaluation study might not be based on a single clinical trial. Alternatively, health economic modelling is an approach to overcome the limitations of conducting an economic evaluation alongside a clinical trial. This thesis documents a health economic study in osteoporosis using modelling approach, with its construction, validation and several applications in the cost-of-illness and cost-effectiveness studies.

1.3 Structure of this thesis

Chapter 1 presents a general introduction to osteoporosis and health economics. In Chapter 2, a systematic review of all osteoporosis health economic models and the evolution of modelling in this field is presented. Chapter 3 details a systematic review and meta-analysis of HSUVs for osteoporosis-related conditions. A standard set of HSUVs is derived for future modellers use in health economic evaluations in osteoporosis.

Chapter 4 describes the documentation and validation of the new osteoporosis health economics model that was developed as a major part of the PhD. Chapter 5 presents the first example of the application of the osteoporosis health economics model. Residual lifetime and 10-years fracture risks for Chinese men and women are estimated using the model. Additionally, international comparisons of residual lifetime fracture risks are discussed.

Chapter 6 describes the second example of model application. Annual fracture numbers and costs are estimated for the Chinese population. Additionally, projection of number and costs of fractures are discussed through to the year of 2050.

Chapter 7 presents the third example of model application: a cost-effectiveness analysis of different osteoporosis screening and treatment strategies. The most cost-effective osteoporosis screening and treatment strategy is recommended.

Finally, Chapter 8 discusses and summarizes the material presented in this thesis.

1.4 References

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Chapter 2: A systematic review of models used in cost-effectiveness analyses of preventing osteoporotic fractures

2.1 Preface

This chapter provides a systematic review of models used in the health economic evaluations of osteoporotic fracture preventions over the past 40 years. This systematic review summarises the evolution of health economic models used in evaluations of clinical approaches aimed at preventing osteoporotic fractures. It demonstrates that models have improved, with medical continuance becoming increasingly recognized as a contributor to health and economic outcomes, as well as advancements in epidemiological data. Lessons learned from the review are implemented in the design of the model developed in Chapter 4.

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The published article of this chapter appears in an appendix to the chapter. It has been removed for copyright or proprietary reasons.

2.2 Abstract

Purpose: Model-based health economic evaluation studies are increasingly used to investigate the cost-effectiveness of osteoporotic fracture preventions and treatments. The objective of this study was to carry out a systematic review of the evolution of health economic models used in the evaluation of osteoporotic fracture preventions.

Methods: Electronic searches within MEDLINE and EMBASE were carried out using a predefined search strategy. Inclusion and exclusion criteria were used to select relevant studies. References listed of included studies were searched to identify any potential study that was not captured in our electronic search. Data on country, interventions, type of fracture prevention, evaluation perspective, type of model, time horizon, fracture sites, expressed costs, types of costs included and effectiveness measurement were extracted.

Results: Seventy-four models were described in 104 publications, of which 69% were European. Earlier models focused mainly on hip, vertebral and wrist fracture, but later models included multiple fracture sites (humerus, pelvis, tibia and other fractures). Modelling techniques have evolved from simple decision trees, through deterministic Markov processes to individual patient simulation models accounting for uncertainty in multiple parameters. Treatment continuance has been increasingly taken into account in the models in the last decade.

Conclusions: Models have evolved in their complexity and emphasis, with medical continuance becoming increasing recognized as a contributor to health and economic outcomes. This evolution may be driven in part by the desire to capture all the important differentiating characteristics of medications under scrutiny, as well as the advancement in epidemiological data relevant to osteoporosis fractures.

2.3 Introduction

Osteoporosis is a major health concern especially in developed countries and countries with an ageing population, with low bone mass and structural deterioration of bone tissue resulting in increased fragility and risk of fractures [1]. It was estimated that 1.9 million Australians had doctor-diagnosed osteoporosis in 2001, and the number was set to grow dramatically over the next two decades to 3 million osteoporosis cases, approximately 13% of the total population in 2021 [2]. Costs of osteoporosis and osteoporotic fractures are one of the major burdens on the healthcare system: 304.3 million Australian dollars were spent on direct health expenditure for osteoporosis in 2004-2005 in Australia, most of which spent on prescribed pharmaceuticals [2, 3]. USA and European Union experienced even higher annual costs of osteoporotic fractures [4-6].

Aside from the financial costs of osteoporosis and osteoporotic fractures, mortality and comorbidity have a major impact in terms of patients' quality of life (QoL). Although osteoporosis does not directly cause death, osteoporotic fractures are associated with excess mortality, both immediately following a fracture and longer term [7, 8]. While hip fractures were estimated to be responsible for most of the burden of osteoporosis-related fractures, recent studies indicated vertebral fractures also play a major role in adversely affecting QoL [8-10].

Modelling techniques have been widely used in cost effectiveness analyses of preventing osteoporotic fractures over the last three decades [11-13]. Models in the healthcare context can be categorized as "empirical" models in which model inputs are retrieved from epidemiological studies, and "theoretical" models in which model parameters are synthesized by statistical techniques, mathematical formulae, or computer simulations [14, 15]. Pure empirical models are rare in reality because of the scarcity of data sources from trials or observational studies. Randomized controlled trials (RCTs) often do not provide head-to-head comparisons of relevant population subgroups [16]. In addition, the time horizon of RCTs is often not long enough to capture all the possible outcomes beyond the trial duration. Therefore, results based on health analytic models give healthcare decision makers useful information even before launching an intervention. This is of great significance when prioritizing health interventions because the scarcity of healthcare resources means only the cost-effective interventions should be subsidized.

Many studies of the cost-effectiveness of preventing osteoporotic fractures have been carried

out over the last three decades. Zethraeus (2002) and colleagues performed a review [17] and an updated review (2007) [18] with a "reference model" created. However, since that review, modelling studies evaluating the health economic impacts of new pharmaceuticals, for instance denosumab [19], have been carried out. Moreover, only studies that defined the effectiveness measure in terms of life years or quality adjusted life years (QALYs) were included in previous reviews rather than including other effectiveness measurements such as fracture averted and life years saved. Therefore, the objective of the study was to carry out an updated review of all published model-based studies to illustrate the evolution of modelling of prevention of osteoporotic fragility fractures, and to summarize the major structural parameters and assumptions within the published models. This review will provide future investigators an overview of progression of cost effectiveness models on osteoporosis related fractures and information on key parameters that affect the robustness of models.

2.4 Methods

This systematic review followed PRISMA guidelines [20]. We performed electronic searches of MEDLINE and EMBASE from 1980 to February 2013. In addition, reference listed in relevant studies were hand searched to identify papers that were not identified in our electronic search.

2.4.1 Search Strategy

We searched using the key words osteoporosis, postmenopausal osteoporosis, osteoporotic fractures, fractures bone, bone mass, cost benefit analysis, costs and cost analysis, utility, quality adjusted life years, life saved, life year saved, life gained, fracture avoided. Details of the specific search strategies used for each database were listed in *Appendix 2B.1*.

2.4.2 Inclusion criteria

The inclusion criteria for the structured review were: studies in humans, studies reporting models of health economic evaluation on primary and/or secondary prevention of osteoporotic fracture, studies that included a cost benefit analysis, cost effectiveness analysis or cost utility analysis on osteoporosis or osteoporotic fractures. We included studies in all ethnic groups globally and in both sexes.

2.4.3 Exclusion criteria

Studies not based on model simulations were excluded as we were looking at the studies that

incorporate modelling techniques on treating or preventing osteoporotic fractures, rather than the focusing on the cost effectiveness or cost utility ratios generated by the models. Other exclusion criteria were

- Publications in languages other than English
- Review articles
- Abstracts with no specified models

We did not evaluate the quality of included studies, as our review was aiming at illustrating and summarizing the evolution of key characteristics of models used in health economic evaluation on osteoporotic fractures preventions and treatments, rather than evaluating the reliability of cost-effectiveness results generated by the models.

2.4.4 Data extraction

Study characteristics, modelling techniques, fracture-related costs as well as health state utility values were extracted. Study characteristics included country, type of fracture prevention (primary or secondary), time horizon, fracture sites, expressed costs, types of costs and effectiveness measurement. To allow comparison of costs between countries and at different time points, costs data from each study were converted into 2013 US dollars using a web-based currency convertor developed by a joint initiative between The Campbell and Cochrane Economics Methods Group (CCEMG) and Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Center) [21]. In addition, we chose the International Monetary Fund (IMF) based Purchasing Power Parity (PPP) value to adjust the exchange rate between countries within the EPPI cost converter [21]. We assumed the year of costs as the time of publication for studies that did not specify the year in which the costs were expressed.

There are several definitions to be clarified: medication compliance, persistence, adherence, as well as offset time effect. Medication compliance or adherence are defined as below: “Medication compliance (synonym: adherence) refers to the act of conforming to the recommendations made by the provider with respect to timing, dosage, and frequency of medication taking [22]”. Medication persistence refers to “the act of conforming to a recommendation of continuing treatment for prescribed length of time” thus can be defined as the duration of time from initiation to discontinuation of therapy [22]. Medication offset time effect refers to residual medication effect after discontinuation of treatment [23].

2.5 Results

The flow chart of study selection for our review was shown in *Figure 2.1*. From 2761 studies identified from our electronic search, 2619 studies remained after removing duplicates. After screening by title and abstract, 109 studies remained. After screening of these full text studies a further 11 studies were excluded because they were either review or non-model based studies. Ninety-eight studies from 1980 to 2013 were then included. A further 6 other studies were identified from the reference lists of included studies, resulting in a final total of 104 included in our review (*see Appendix 2B.2*). Model-based health economic evaluations on osteoporotic fracture prevention were published exponentially in the last decade (*Figure 2.2*). Six of 104 studies involved multiple country evaluation using the same model therefore there were a total of 18 countries with 124 assessments involved by splitting the multi-county studies.

Included studies are detailed in *Appendix 2B.3 Table 1*. Seventy-four models were used within 104 studies. Some studies shared model structure for data analyses, for example Johnell (2003) [24] used the same model structure as Borgstrom (2006) [25] and Strom (2007) [26]. Tosteson (2001) [27] used the same model structure as Thompson (2010) [28] and Alzahouri (2013) [29]. Eighty-five (69%) of studies identified were based in a European setting, followed by the US and Canadian (n=29, 23%), six from Asia (5%) and 4 from Australia (3%). Hip fracture was the most frequently included fracture site: 101 studies (97%) included hip fracture, 79 studies (76%) included vertebral fracture and 69 (66%) included wrist fracture. Furthermore, 44 (42%) of studies included other fractures such as pelvis fracture, humerus fracture, and tibia fracture.

There were 12 studies that incorporated established osteoporotic fractures at baseline and were categorised as secondary fracture prevention models. Most of the models were designed to simulate the prevention of first and subsequent fractures; i.e.: both primary and secondary fracture prevention.

Thirty models (29%) used a societal perspective that incorporated all costs including direct costs, indirect costs as well as costs of added life years. However, 14 studies stated that the societal perspective was taken, but did not take indirect costs into consideration. Sixty-three studies (60%) chose narrower perspectives such as third-party payer, patients and healthcare. Moreover, there were 11 studies (11%) that did not clearly state the perspective of the evaluation.

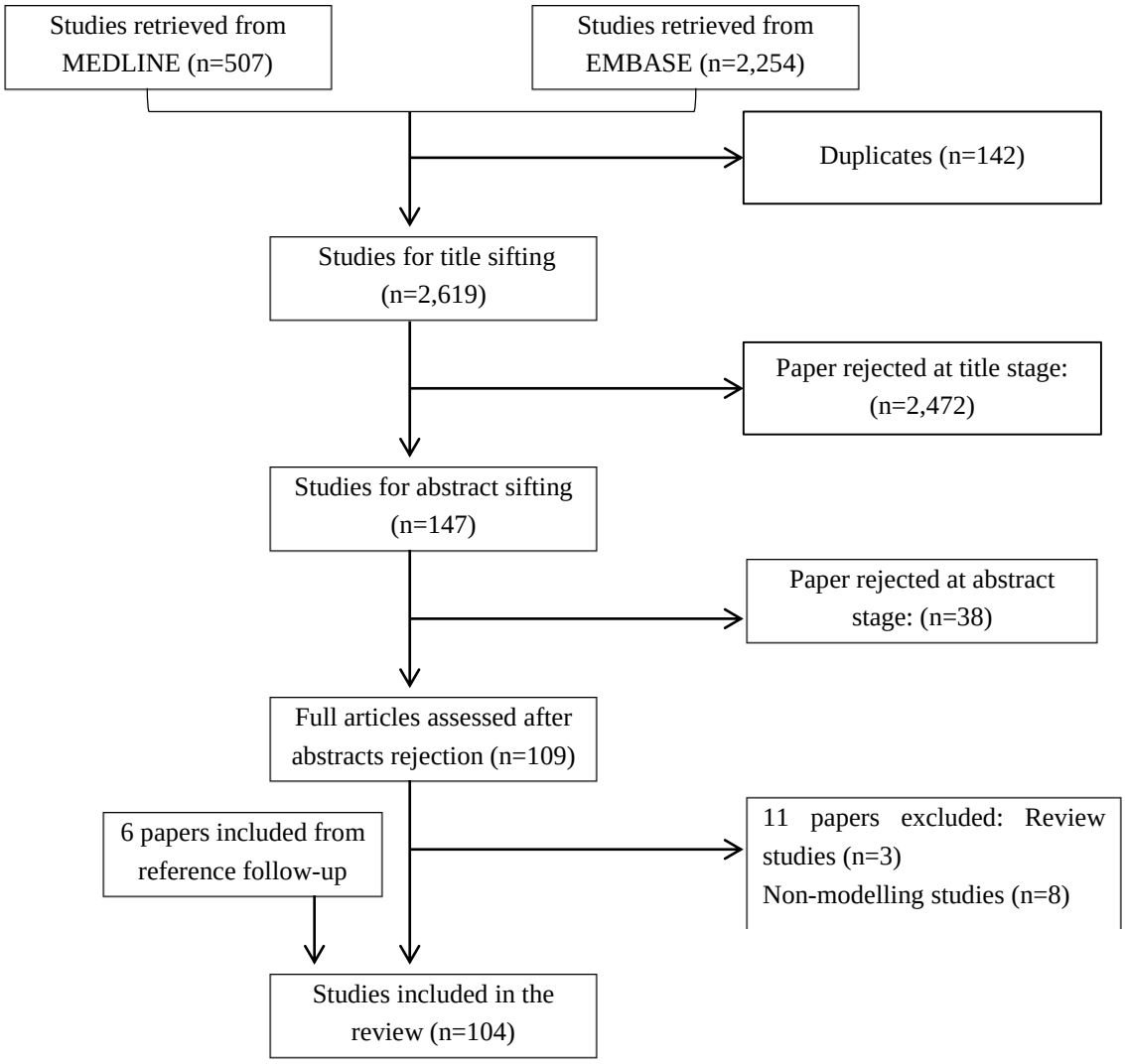

Figure 2.1 Flow diagram for study selection

Ninety-three studies (89%) used Markov models. Thirty five studies applied exact modelling time horizon such as 10 years and 15 years, especially in the earlier studies (10 out of 13 studies between 1980 and 1999), while the remaining studies chose "lifetime" modelling

horizon, running the model until all simulated patients had died to capture all possible costs and patient outcomes associated with the target intervention.

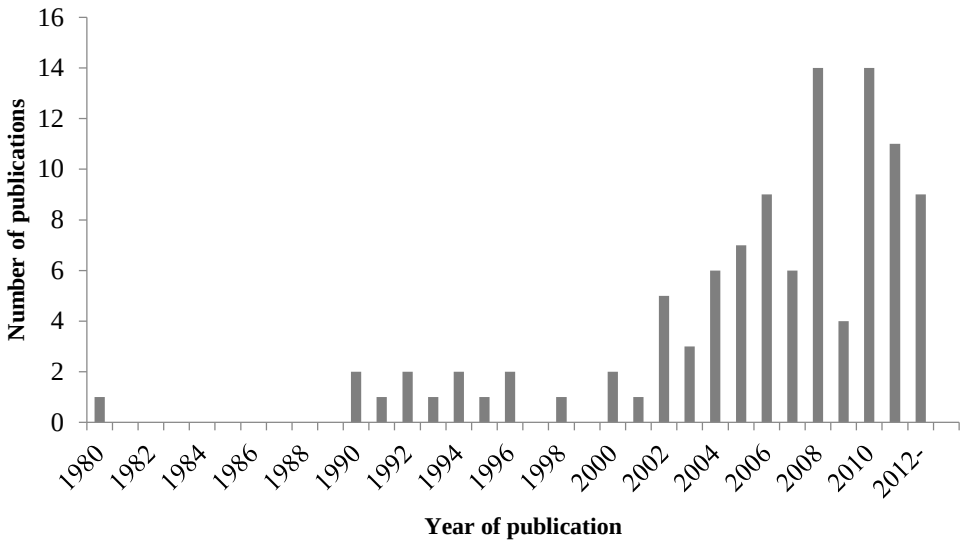

Figure 2.2 Number of publications of modelling studies from 1980-2012

Early studies typically performed univariate sensitivity analyses to assess the robustness of their findings. The first study identified that used probabilistic sensitivity analysis (PSA), sampling from distributions to deal with uncertainties around multiple parameters, was Fleurence (2004) [30]. PSA was increasingly used thereafter (*Table 2.1*).

Appendix 2B.3 Table 2 summarized the costs of fracture categorized by country and specified by fracture sites. In line with the fracture sites in *Appendix 2B.3 Table 1*, the costs of fracture were also divided into hip fracture costs, vertebral fracture costs, wrist fracture costs and other fracture costs. Age-specific costs were frequently used for the first year costs after hip and vertebral fractures [12, 31, 32]. Second year costs of hip fracture depended on residential status, fractures resulting in nursing home admissions in particular tended to have higher costs [12, 33]. For example, Nayak and colleagues [34] assumed 60% of the patients with hip fracture would be admitted to nursing home and annual cost for nursing home was 74,846 US dollars in 2010 values.

Table 2.1. Evolution of modelling characteristics from 1980 to 2013

	1980-1985	1986-1990	1991-1995	1996-2000	2001-2005	2006-2010	2011- 2013
Fracture included in the models							
Hip fracture	1 (100%) [a]	2 (100%)	7 (100%)	4 (80%)	21 (95%)	46 (98%)	20 (100%)
Vertebral fracture	0 (0%)	0 (0%)	3 (43%)	2 (40%)	19 (86%)	39 (83%)	16 (80%)
Wrist fracture	1 (0%)	0 (0%)	4 (57%)	1 (20%)	16 (73%)	33 (70%)	14 (70%)
Other fracture	0 (0%)	0 (0%)	2 (29%)	1 (20%)	8 (36%)	24 (51%)	9 (45%)
Model type							
Simple decision tree model	0 (0%)	0 (0%)	4 (57%)	0 (0%)	2 (9%)	3 (6%)	1 (5%)
Memoryless Markov model [b]	0 (0%)	1 (50%)	3 (43%)	5 (100%)	17 (77%)	30 (64%)	11 (55%)
Markov model with memory [c]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (9%)	14 (30%)	8 (40%)
Medicine Continuance [d]	0 (0%)	0 (0%)	2 (29%)	2 (40%)	2 (9%)	17 (36%)	9 (45%)
Offset time effect [e]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (23%)	13 (28%)	5 (25%)
PSA [f]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (36%)	27 (57%)	9 (45%)
Total	**1**	**2**	**7**	**5**	**22**	**47**	**20**

[a] Number of studies and the percentage of that period. [b] Markov cohort models which the subsequent state was independent from the previous state. [c] Markov cohort models that incorporated tunnel technique or tracker, or individual state-transit model. [d] medicine compliance and persistence. [e] residual medication effect after discontinuation of treatment. [f] PSA Probabilistic sensitivity analysis.

The most frequently (88%) used effectiveness measurements were QALYs that incorporated both length and quality of life; the remaining studies used health effects such as life years saved, fractures averted or years free from fracture (*Appendix 2B.3 Table 1*). A detailed description of utility values is given in *Appendix 2B.3 Table 3*. Utility values were generally divided into those in the first year after fracture and those in the second-plus years after fracture; exact utility values were frequently assigned in most of studies prior to 2000 whilst utility multipliers were frequently used after 2000 to calculate the QALY relative to healthy population in the same age group. Clinical vertebral fractures were shown to have higher impact compared with hip fractures in terms of health utility. Wrist fractures were consistently reported as having little/no impact on health utility from the second year following initial fractures. The impacts of multiple fractures firstly addressed by Tosteson and colleagues in 2001[35], when they found that women with both hip and vertebral fracture

had the lowest utility value. This contradicted with previous studies that recognized hip fracture as the "worst" situation and influenced later researchers [36-38]. However, there were other ways to adapt utilities for multiple fractures. Wasserfallen and colleagues [39] used higher disutility when patients got subsequent fractures. Hiligsmann and colleagues [40, 41] used additive utility, which was the sum of impacts related to each of the fracture, for multiple fractures impact evaluation. Murphy and colleagues [42] used multiplicative utility for multiple fractures utility evaluation: for example, the utility value for a patient with both hip and vertebral fracture equaled to utility value for hip fracture multiplied by utility value for vertebral fracture. For a second fracture in the same site as the initial fracture, Hiligsmann and colleagues [40, 41] discounted the impact of second fracture as 50% of that of initial fracture.

Twenty-four studies took "extraskeletal effects" due to treatments into account. Excess mortality after fractures was accounted for in 59 out of 104 reviewed studies, expressed as mortality rate or mortality relative risk to that of general population or population free from fractures. It was argued that not all the excess mortality was associated with fracture events, therefore in many studies a discounted excess mortality was used to adjust the mortality directly related to fracture events. For instance, 25% was assumed as the percentage of the excess mortality that directly caused by fractures [43-45].

Higher relative risk of second fracture following first fracture was assumed in studies of secondary fracture prevention. However, the reviewed studies reported a wide range of relative risks of different fracture sites, and even varied within the same fracture site [13, 46]. In addition, relative risk of second fracture in younger age was assumed to be higher comparing with that in older population. For example, relative risk of second hip fracture following an initial hip fracture was 7.14 for age younger than 70 years old whilst for population aged older than 70 years that relative risk of second hip fracture was 2.24 [37].

The effects of many pharmaceutical interventions were assumed not to cease immediately after discontinuation of therapy and the residual effects, or so-called offset time effects, conversely enhance the cost effectiveness in many of the more recent models, particularly those in which bisphosphonates were assessed. Studies constantly assumed the offset time effect declined in a linear manner after the discontinuation of treatments for an additional 5 years [32, 39, 43, 47-51]. Offset time effect of treatment was widely considered in models after 2000 (*Table 2.1*) and was discussed in sensitivity analyses. Offset times ranged from

one year to five years depended on the assessed pharmaceuticals and declined in a linear manner until no residual effect of treatment was assumed after the discontinuation of the treatment [31, 43, 51, 52].

Medical compliance and persistence were also included in some recent models as a critical parameter affecting the cost effectiveness of an intervention. Consequently, patients with poor persistence and compliance were assumed to have higher risk of fracture comparing with that of full persistence and compliance. Effect of compliance was first applied, to our knowledge, in Daly and colleagues' model in 1992 [53] and then sporadically included thereafter (*Table 2.1*). Studies generally included medication compliance after Kanis and colleagues' Health Technology Assessment report in 2002 [11]. Whilst medical compliance and persistence were widely discussed, there were some conflicts in terms of definitions [29, 39, 45]. The value of compliance and persistence also depends on the assessed treatment; it was assumed almost half of patients dropped out from bisphosphonates use within the first 6 months [28, 38, 40]. Hiligsmann and colleagues found the QALY gains with real world adherence only represented 30.2%, 32.1% and 34.2% of the episodes estimated with full alendronate compliance for the patients aged 55, 65 and 75 years [54].

2.6 Discussion

New and potentially costly pharmaceuticals for prevention of osteoporosis-related fractures are being introduced. Due to health care budget constraint, reimbursement agencies should only subsidize interventions that represent good value for money; i.e. are cost-effective. Due to the relative short term of nature of clinical trials, modelling has been used as a complementary decision analysis tool in the assessment of cost effectiveness of prevention of osteoporotic fractures in past decades. Models have evolved in their complexity and emphasis, with medical continuance becoming increasing recognized as a contributor to health and economic outcomes. Good quality models that incorporate uncertainties around the models simulate the treatment or prevention outcomes more precisely. This review provides an outline in terms of the evolution of modelling in preventing osteoporotic fractures with a recommendation of what parameters should be incorporated in model-based health economic evaluations.

Cost and utility data in model-based cost effectiveness analyses were often retrieved from clinical trials, specifically, categories of costs included in the model should be in line with the

evaluation perspective. Studies on a societal perspective should incorporate all costs including direct and indirect cost from the disease. Studies from a healthcare perspective, however, do not necessarily include indirect costs. In osteoporotic fractures context, it was necessary to divide the costs of fracture into first year cost after fracture and second year cost. In addition, costs were highly depended on severity of fractures. Nursing home hip fractures incurred higher costs in the second and following years than the first year costs that were basically costs of treatment. Fractures that in older age incurred higher costs than that in younger age. Similarly, utilities should split into first year utility and second year utility after fractures by utility decrements or utility multiplier relative to the utility of population free from fractures. As most of the patients healed from acute fracture events and treatment improve the utility on subsequent years following fractures.

Studies had shown that the white women have higher osteoporotic fracture risks than other ethnic women groups [55, 56]; this is in line with our review as most of the reviewed studies were targeted on the Caucasian women. Hip, vertebral (including clinical vertebral and morphometric) and wrist fractures were the most popular studied fracture sites as they were the most commonly osteoporotic fractures, representing 82% of all osteoporotic fracture events [6]. However, other fracture sites such as proximal humerus, proximal tibia, distal femur and pelvis were also investigated in models [49, 57].

The use of models that evaluated cost effectiveness of medical interventions has continued in health economics in the past decades. Structures of the model should reflect the health condition or clinical pathway of assessed diseases [58-60], decision tree model and Markov model are commonly used structures in health economics. A decision tree model simulates the prognosis of a patient following the choice of a management strategy; it is simple to be understood but sophisticated enough to cover the essentials of the problem. Markov models are useful when a decision problem involves risk that is continuous over time [61], and when important events repeat over time. Therefore, Markov models are particularly useful in evaluations involving chronic diseases [62]. This was proven in our review as the majority of the reviewed studies chose Markov model. There are three ways to evaluate Markov model: matrix algebra, cohort simulation and Monte Carlo simulation [61]. Most of our reviewed studies either chose cohort simulation or Monte Carlo simulation. In Markov cohort model, a whole cohort of patients through the model simultaneously, the subsequent state is independent from the previous state, which is known as “memoryless” nature, or “Markovian

assumption", of Markov cohort [63]. Osteoporotic fracture probability as well as osteoporotic fracture related mortality, however, is assumed to be highly dependent on the previous health state [7]. Therefore, tunnel technique [32, 51] or tracker [41] was manipulated in many of the reviewed studies to overcome this flaw. Another way to overcome the memorylessness is individual (or Monte Carlo) simulation, whereas a large number of patients through the model individually and the transit probability at the chance node depends on the previous state. There were numbers of examples [13, 33, 34, 64] using individual simulation in our review. To our knowledge, there was no study looking at the difference in terms of cost effectiveness results using Markov cohort simulation comparing with Monte Carlo simulation.

We noted that some studies [65, 66] in our review claimed a societal perspective but did not consider indirect costs. Furthermore, around 11% of studies did not describe the perspective of the evaluation. The scope or perspective of a decision analytic model should be clearly stated and in line with the study objective [67]. A societal perspective that "considers everyone affected by the intervention and counts all significant health outcomes and costs that flow from it, regardless of who experiences the outcomes or costs" [68] should incorporate all relevant costs, which are direct costs, indirect costs and costs on added life years and this, has been recommended in many country-specific economic guidelines [59, 69], but not all [70]. Categories of costs in the model should be in line with the evaluation perspective and indirect cost should be considered in health economic studies on osteoporotic fracture prevention at least in working population. It could be argued this is not necessary in older populations (not of working age) where no productivity loss be assumed [71]. Failure to incorporate indirect costs may result in biased estimates of cost effectiveness as found in recent studies where indirect costs contribute 29.2% [72] and 34% [5] of total costs under a societal perspective.

The defined modelling time horizon should be specified [73] and long enough to encapsulate all significant clinical and economic outcomes [59]. A lifetime modelling horizon potentially captures all the necessary differences in long-term costs and effects between the treatments especially in chronic diseases. Specifically, the analyst should make distinction between the treatment continuance and the time horizon of the model [74]. Though it was argued time horizon should take the clinical prognosis in consideration [59] and match that of the actual process [75], lifetime modelling time horizon is highly recommended in numbers of guidelines [68, 70].

Subsequent fractures may occur within the modelling time horizon therefore relative risks of second and subsequent fractures need to be accounted for. Klotzbuecher and colleagues (2000) [76] review on relative risk of future fractures following initial fracture had been cited and used in the National Institute for Health and Care Excellence (NICE) model [12], which indicated that an initial fracture greatly increased the risk of subsequent fracture, at the same as well as other fracture sites, independently of bone mass density. Johnell and colleagues (2004) [77] carried out a study aiming at examining the pattern of fracture risk after an initial osteoporotic fracture; their results indicated fracture rates following an initial fracture were substantially increased in the immediate post-fracture period. Their findings were used by many cost effectiveness studies base on Swedish setting [78, 79]. Given the clinical significance of fracture status, a population specific relative risk of fracture should be fitted in model included second and subsequent fractures.

Adverse events, or "extraskeletal" effects included in models influenced cost-effectiveness outcomes, especially in early studies on hormone replacement therapies. Breast cancer, endometrial cancer, cardiovascular diseases and thromboembolism events were the most mentioned extraskeletal effects [53, 80-86]. However, extraskeletal effects were rarely discussed after the cessation of hormone replacement therapy (HRT) for long-term osteoporotic fractures prevention [87] as HRT treatment involved in higher risk for coronary heart disease, pulmonary embolism, stroke and invasive breast cancer though it was a protection for colorectal cancer and hip fracture. The reasons behind this phenomenon were two-fold: paucity of evidence to prove the evaluated medication had adverse effect on human, for example, osteosarcomas cases were found in rats given parathyroid hormone, but no human case was found in Neer's study [88]; or side effects were mild and could be easily averted [89]. Extraskeletal effects were recommended in modelling: firstly, costs as well as effectiveness from adverse events would affect the cost effectiveness. Woo and colleagues [90] argued the degree of risk of osteonecrosis for patients taking oral bisphosphonate was uncertain thus warrants careful monitoring, hence costs of monitoring were encouraged to be added for studies evaluating bisphosphonates. Secondly, extraskeletal events in some cases prompt the discontinuation of therapies [91, 92] that causally decreased the efficacy of medication.

Mortality after osteoporotic fractures was estimated to be higher than the fracture-free population, especially for immediate mortalities after hip, vertebral and shoulder fractures

[93], but not following forearm fractures [8]. Excess mortality was estimated not only related to fracture events, but also the comorbidity factors of osteoporotic fracture patients [94]. Numbers of the reviewed studies were in line with the published findings, causal mortality of osteoporotic fracture patients were estimated ranged from 23% to 30% [39, 51, 54].

Persistence, compliance and adherence with medications was widely discussed in reviewed studies, particularly after 2002, and proven to affect the cost effectiveness of assessed interventions to a substantially [95]. These factors play an important role in modelling on osteoporotic fracture prevention, as patients tend to be not fully adherent or persistent with medicines [44] as well as non-pharmaceutical interventions such as hip protectors [96]. As a consequence, there may be complex interactions between continuing effectiveness of an intervention and the impact of medical continuation on costs.

2.7 Conclusions

A good modelling study should be in line with the criteria of critical appraisals, such as BMJ checklist [97] and CHEERS statement [98]. In addition, a number of points are particularly important in cost effectiveness modelling of osteoporotic fracture prevention: Markov individual state-transition model that overcomes the memorylessness nature of Markov cohort model is preferred in order to capture all the interactions between events and changed risks of future fractures and mortality. When a Markov cohort model is implemented, tracker variables, tunnel states or other methods for building in memory are required. Modelling time horizon should be long enough to capture all possible costs and effectiveness; hence lifetime horizon is preferable. Extraskeletal effects of treatment should be considered in the analysis as evidence suggests that adverse events strongly affect costs, treatment continuance and quality of life. The possibility of more than one fracture should be considered in long time horizon modelling. Furthermore, mortality risk following fractures should be based on evidence from the population assessed. It is important to take medicine continuance into account, and it should be tested in sensitivity analysis. Offset time effects needs to be considered for non-adherent or non-persistent patients. Cost and effectiveness data should be divided into at least first year and subsequent year costs and utilities.

Modelling will consistently play an important role in health economic evaluations of osteoporotic fracture prevention. It complements the clinical trials to capture long-term costs and effectiveness and by comparing different treatment alternatives to inform the policy

makers funding the treatment that best worth the value. Therefore, an osteoporosis-related-fractures model should be transparent to reviewers as well as to policy makers, built by independent researchers to minimize the risk of bias, and be constructed in line with health economic guidelines.

2.8 Postscript

In this chapter, the evolution of health economic modelling in the field of osteoporosis has been summarized. In addition, recommendations for future models are provided and have been incorporated in the new osteoporosis health economics model that was subsequently developed and is documented in Chapter 4:

- Evolving patient characteristics are important when determining the transition probabilities and therefore should be recorded using modelling techniques such as tracker variables and tunnel states. Tracker variables were subsequently used in the model, for example, "number of fractures" was used to determine whether the patient has a fracture history and the number of fracture that the patient has sustained; "time after last fracture" was used to determine the time elapsed from last fracture. Consequently, microsimulation was used to account for the tracker variables to calculate the cost, effectiveness and cost-effectiveness.
- Lifetime horizon was adopted in our analyses to capture long term costs, effectiveness of different treatments and prevention strategies. In addition, costs and health state utility values for fractured patients were differentiated in first-year and subsequent years after fracture.
- Impact of medication persistent, adherence and offset time effect was fully incorporated in the subsequent development of the osteoporosis model. In addition, the effect of changes in these parameters on cost, effectiveness and cost-effectiveness were tested.
- In addition to the above considerations, a Bayesian approach was implemented to account for the prior and posterior probabilities for the osteoporosis screening health economics model. This is the first application of Bayesian revision in an osteoporosis health economics model.

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Appendix 2B.1 Search strategy in MEDLINE and EMBASE

For MEDLINE:

1. osteoporosis, postmenopausal

2. osteoporosis OR osteoporotic fractures OR fractures, bone OR bone mass

3. cost-benefit analysis OR costs and cost analysis OR utility OR quality-adjusted life years OR life saved OR life year saved OR life gained OR life years gained OR fractures avoided

4. #1 AND #2 AND #3

For EMBASE:

1. 'osteoporosis'/exp OR 'postmenopause osteoporosis'/exp

2. 'osteoporosis'/de OR 'fragility fracture'/de OR 'bone mass'/de OR 'wrist fracture'/de OR 'cervical spine fracture'/de OR 'colles fracture'/de OR 'forearm fracture'/de OR 'spine fracture'/de OR 'hip fracture'/de

3. 'cost effectiveness analysis'/exp OR 'cost utility analysis'/exp OR 'cost'/exp

4. #1 AND #2 AND #3

Appendix 2B.2 Studies included in the systematic review

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Appendix 2B.3 Table 1: Overview of studies included

Study	Country	Assessed intervention	Type of fracture prevention		Evaluation perspective	Type of model	Time horizon	Fracture sites				Costs unit	Costs		Effectiveness measurement
			P	S				Hip	Vertebral	Wrist	Other		D	I	
Weinstein 1980	USA	HRT	Y	Y	societal	cost effectiveness model	10 yrs	Y	N	Y	N	USD	Y	N	LYs gained and QALE
Tosteson 1990	USA	screening and HRT	Y	Y	societal	Markov model	15 yrs	Y	N	N	N	1987 USD	Y	N	Life expectancy and QALE
Weinstein 1990	USA	HRT	Y	Y	societal	NA	5 and 15 yrs	Y	N	N	N	1988 USD	Y	N	quality adjusted life expectancy (QALE)
Tosteson 1991	USA	HRT	Y	Y	patients	Markov model	10 and 15 yrs	Y	N	N	N	1990 USD	Y	N	LYs saved and quality adjusted LYs saved
Cheung 1992	Australia	HRT	Y	Y	Health care	cost effectiveness model	lifetime	Y	N	Y	N	1988 AUD	Y	N	QALY
Daly 1992	UK	HRT	Y	Y	National Health Service	computer model	10 yrs	Y	Y	Y	Y	1989/1990 Pound	Y	Y	LYs gained and QALY
Torgerson 1993	UK	HRT and calcium	Y	Y	Health care	cost effectiveness model	10 yrs	Y	N	N	N	Pound	Y	N	fractures averted
Chrischilles 1994	USA	not specified	Y	Y	societal	Markov model	life time	Y	Y	Y	N	1992 USD	Y	N	life expectancy increased
Geelhoed 1994	Australia	HRT and lifestyle intervention	Y	Y	Health care	Markov model	50 yrs	Y	N	N	N	1991 AUD	Y	N	QALY
Jonsson 1995	Denmark	not specified	Y	Y	societal	decision tree model	5 yrs	Y	Y	Y	Y	SEK	Y	N	percentage reduction in annual fracture rate, LYs gained and QALY

Appendix 2B.3 Table 1: Overview of studies included

Study	Country	Assessed intervention	Type of fracture prevention		Evaluation perspective	Type of model	Time horizon	Fracture sites				Costs unit	Costs		Effectiveness measurement
			P	S				Hip	Vertebral	Wrist	Other		D	I	
Ankjaer-Jensen 1996	Denmark	calcium , etidronate, calcitonin and HRT	Y	Y	societal	simulation model	life time	Y	Y	Y	N	DKK	Y	Y	reduction in number of hip fractures
Torgerson 1996	UK	Vitamin D, thiazide diuretics, HRT, calcium, calcitonin	Y	Y	NA	computer model	5 yrs	Y	N	N	N	Pound	Y	N	Fx reduction
Rosner 1998	Canada	bisphosphonates, OHT, calcium	Y	Y	societal	decision tree model	3 yrs	N	Y	N	N	1998 CAD	Y	Y	vertebral Fx averted and QALY
Sendi 2000	Switzerland	No intervention	Y	Y	NA	Markov model	life time	Y	N	N	N	CHF	Y	N	expected survival and distribution of residual lifetimes
Solomon 2000	USA	screening, alendronate, ERT, etidronate	Y	Y	societal	Markov model	life time	Y	N	N	Y	1998 USD	Y	N	QALY
Willis 2001	Sweden	tibolone	Y	Y	national health system	Markov model	25 yrs	Y	Y	Y	N	1998 SEK	Y	N	reduction of Fx and QALY
Grima 2002	USA	resedronate, alendronate	Y	Y	NA	Markov state-transition model	life time	Y	Y	N	N	2000 USD	Y	N	fracture averted and QALY gained
Iglesias 2002	UK	risedronate	Y	Y	NA	Markov state-transition model	life time	Y	Y	Y	N	1999 Pound	Y	N	QALY

Appendix 2B.3 Table 1: Overview of studies included

Study	Country	Assessed intervention	Type of fracture prevention		Evaluation perspective	Type of model	Time horizon	Fracture sites				Costs unit	Costs		Effectiveness measurement
			P	S				Hip	Vertebral	Wrist	Other		D	I	
Kanis 2002	UK	pharmaceutical agents	Y	Y	NHS and social care	Markov model	lifetime	Y	Y	Y	Y	Pound	Y	N	QALY
Nagata-Kobayashi 2002	Japan	HRT	Y	Y	societal	Markov state-transition model	30 yrs	Y	N	N	N	2000 Yen	Y	N	QALY
Willis 2002	Sweden	calcium and vitamin D_3	Y	Y	national healthcare and social welfare system	Markov model	until 90 yrs old had been reached	Y	N	N	N	2000 SEK	Y	N	QALY and LYs gained
Brecht 2003	Germany	risedronate	N	Y	German social insurance	Markov state-transition model	10 yrs	Y	Y	Y	Y	2000 Euro	Y	N	QALY
Buckley 2003	USA	calcium and vitamin D, etidronate and alendronate	Y	Y	societal	decision analytic model	10 yrs and life time	N	Y	N	N	2000 USD	Y	Y	Fx avoided
Johnell 2003	Sweden	alendronate	N	Y	Health policy	Markov model	5 yrs treatment+5 yrs fall time	Y	Y	Y	N	2000 SEK	Y	N	QALY
Borgstrom 2004	Sweden	raloxifene	Y	Y	healthcare and societal	Markov model	lifetime	Y	Y	Y	N	2001 SEK	Y	Y	QALY and LYs gained
Brecht 2004	Germany	risedronate, alendronate and raloxifene	Y	Y	health payer	Markov state-transition model	10 yrs	Y	Y	N	N	Euro	Y	N	QALY
Fleurence 2004	UK	VD and calcium and hip protectors	Y	Y	National Health Service	Markov model	life time	Y	Y	Y	N	2000 USD	Y	N	QALY

Appendix 2B.3 Table 1: Overview of studies included

Study	Country	Assessed intervention	Type of fracture prevention		Evaluation perspective	Type of model	Time horizon	Fracture sites				Costs unit	Costs		Effectiveness measurement
			P	S				Hip	Vertebral	Wrist	Other		D	I	
Kanis 2004	UK	risedronate	Y	Y	Health care	Markov model	life time	Y	Y	Y	N	2000/01 Pound	Y	N	QALY and LYs gained
Singh 2004	Canada	hip protectors	Y	Y	societal	decision analytic model	lifetime	Y	N	N	N	2001 CAD	Y	N	QALY
Stevenson 2004	UK	alendronate, calcitonin, HRT and raloxifene	Y	Y	NA	Gaussian process model	10 yrs	Y	Y	Y	Y	2002 Pound	Y	N	QALY and LYs gained
Christensen 2005	Denmark	alendronate	Y	Y	health-care sector	Markov cohort simulation model	life time	Y	Y	Y	N	2002 DKK	Y	N	QALY gained, LYs gained, Fx avoided
Kanis 2005	UK	raloxifene	Y	Y	Health care	Markov model		Y	Y	Y	N	2002 Pound	Y	N	QALY and LYs gained
Schousboe 2005	USA	alendronate	Y	Y	societal	Markov model	life time	Y	Y	Y	Y	2001 USD	Y	Y	QALY
Schousboe 2005	USA	alendronate	Y	Y	societal	Markov model	life time	Y	Y	Y	Y	2001 USD	Y	N	QALY
Schousboe 2005	USA	alendronate	Y	Y	societal	Markov model	life time	Y	Y	Y	Y	2001 USD	Y	Y	QALY
Stevenson 2005	UK	bisphosphonates, raloxifene, oestrogen	Y	Y	Health care	Individual state transition model	10 yrs	Y	Y	Y	Y	2001/2002 Pound	Y	N	QALY
Zethraeus 2005	Sweden	HRT	Y	Y	societal	Individual state transition model	50 yrs	Y	Y	Y	Y	2003 SEK	Y	Y	QALY
Borgstrom 2006	Sweden, Finland, Belgium, Spain	risedronate	Y	Y	Health care	Markov cohort model	life time	Y	Y	Y	Y	2003/04 Euro	Y	N	LYs gained and QALY

Appendix 2B.3 Table 1: Overview of studies included

Study	Country	Assessed intervention	Type of fracture prevention		Evaluation perspective	Type of model	Time horizon	Fracture sites				Costs unit	Costs		Effectiveness measurement
			P	S				Hip	Vertebral	Wrist	Other		D	I	
Borgstrom 2006	Australia ,Germany, Japan, Sweden, Spain and UK	bisphosphonate	Y	Y	societal	Markov cohort model	life time	Y	N	N	N	2004 USD	Y	Y	QALY
Borgstrom 2006	Sweden	Strontium ranelate	Y	Y	societal	Markov cohort model	life time	Y	Y	Y	Y	2004 SEK	Y	Y	QALY
Goeree 2006	Canada	alendronate, etidronate, risedronate and raloxifene	Y	Y	Provincial Government	Markov model	30 yrs	Y	Y	N	N	2005 CAD	Y	N	LYs and QALY
Liu 2006	USA	Teriparatide, alendronate	Y	Y	societal	Microsimulation	life time	Y	Y	Y	N	2003 USD	Y	Y	QALY
Lundkvist 2006	Sweden	teriparatide in addition to vitamin D and calcium	Y	Y	societal	Microsimulation	life time	Y	Y	Y	Y	2003 Euro	Y	N	QALY
Mobley 2006	USA	HRT, raloxifene, alendronate	Y	Y	medical care	Markov model	life time	Y	Y	N	N	2002 USD	Y	N	Fx avoided, LYs saved and QALY
Panichkul 2006	Thailand	screening	Y	Y	individual	decision tree	5 yrs	Y	N	N	N	2004 THB	Y	Y	numbers of perimenopausal women free from fracture
Pfister 2006	USA	calcitonin, raloxifene, bisphosphonates and PTH	Y	Y	health payer	decision tree	5 yrs	Y	Y	N	Y	2000 USD	Y	N	QALY
Earnshaw 2007	USA	bisphosphonates	Y	Y	third party payer	Markov model	life time	Y	Y	Y	N	2006 USD	Y	N	LYs and QALY

Appendix 2B.3 Table 1: Overview of studies included

Study	Country	Assessed intervention	Type of fracture prevention		Evaluation perspective	Type of model	Time horizon	Fracture sites				Costs unit	Costs		Effectiveness measurement
			P	S				Hip	Vertebral	Wrist	Other		D	I	
Schott 2007	France	screening	Y	Y	health care system	Markov state-transition model	10 yrs	Y	N	N	N	Euro	Y	N	number of years without a hip Fx gained
Schwenkglenks 2007	Switzerland	alendronate	Y	Y	health care system	Markov state-transition model	life time	Y	Y	Y	N	2006 CHF	Y	N	QALY
Stevenson 2007	UK	Strontium ranelate	Y	Y	societal	state transition model	10 yrs	Y	Y	Y	Y	2003/04 Pound	Y	N	QALY
Strom 2007	Belgium, Denmark, France, Germany, Italy, Norway, Spain, Sweden, UK	alendronate	Y	Y	Health care	Markov cohort model	lifetime	Y	Y	Y	N	2004 Euro	Y	N	QALY
van Staa 2007	UK	bisphosphonates	Y	Y	NA	individual patient-based model	10 yrs	Y	Y	Y	Y	Pound	Y	N	QALY
Ding 2008	Japan	risedronate	Y	Y	NA	state transition model	3 yrs	N	Y	N	Y	USD	Y	N	QALY
Gandjour 2008	Germany	hip protectors	Y	Y	societal and statutory health insurance	Markov cohort model	17 yrs	Y	N	N	N	2004 Euro	Y	N	QALY
Grima 2008	Canada	risedronate and alendronate	Y	Y	provincial Ministry of Health	State-transition model	5 yrs	Y	N	N	N	2006 CAD	Y	N	QALY

Appendix 2B.3 Table 1: Overview of studies included

Study	Country	Assessed intervention	Type of fracture prevention		Evaluation perspective	Type of model	Time horizon	Fracture sites				Costs unit	Costs		Effectiveness measurement
			P	S				Hip	Vertebral	Wrist	Other		D	I	
Hiligsmann 2008	Belgium	prescreening using quantitative ultrasonometry	Y	Y	health care	Markov microsimul-ation model	life time	Y	Y	Y	Y	2006 Euro	Y	Y	QALY
Jansen 2008	UK and the Netherlands	alendronate and cholecalciferol	Y	Y	healthcare payer	Markov model	10 yrs	Y	Y	Y	Y	2004 Pound	Y	N	QALY
Johansson 2008	Sweden	non-pharmaceutical prevention	Y	N	societal	Markov model	lifetime	Y	N	N	N	2004 SEK	Y	N	QALY
Kanis 2008	UK	bisphosphonate	Y	Y	health care	Markov cohort model	lifetime	Y	Y	Y	Y	Pound	Y	N	QALY
Kreck 2008	Germany	ibandronate	Y	Y	societal	Markov model	10 yrs	Y	Y	Y	N	2004 Euro	Y	Y	QALY
Lekander 2008	Sweden, UK and US	Hormone therapy	Y	Y	societal	state transition model	lifetime	Y	Y	Y	N	2006 USD	Y	Y	QALY
Mueller 2008	Germany	screening	Y	Y	statutory health system	Markov model	life time	Y	Y	Y	N	2006 Euro	Y	N	QALY
Mueller 2008	Germany	screening, bisphosphonates	Y	Y	statutory health system	Markov state-transition model	life time	Y	Y	Y	N	2006 Euro	Y	N	QALY
Tosteson 2008	USA	risedronate compared with alendronate, ibandronate, and teriparatide	N	Y	Health policy	Markov state-transition model	10 yrs	Y	Y	N	N	2005 USD	Y	N	QALY
Tosteson 2008	USA	bisphosphonate	Y	Y	NA	State-transition model	lifetime	Y	Y	Y	Y	2005 USD	Y	N	QALY and hip Fx averted

Appendix 2B.3 Table 1: Overview of studies included

Study	Country	Assessed intervention	Type of fracture prevention		Evaluation perspective	Type of model	Time horizon	Fracture sites				Costs unit	Costs		Effectiveness measurement
			P	S				Hip	Vertebral	Wrist	Other		D	I	
Wasserfallen 2008	Switzerland	risedronate	N	Y	Health care	Markov model	lifetime	Y	Y	Y	N	2005 Euro	Y	N	QALY
Danese 2009	USA	bisphosphonates	N	Y	NA	Monte Carlo simulation model	lifetime	Y	Y	Y	N	2008 USD	Y	N	lifetime number of fx averted
Hiligsmann 2009	Belgium	bisphosphonate	Y	Y	direct health-care cost	Markov microsimul-ation model	lifetime	Y	Y	Y	Y	2006 Euro	Y	N	QALY
Majumdar 2009	Canada	alendronate	N	Y	third party payer	Markov dedision-analytic model	lifetime	Y	Y	Y	N	2006 CAD	Y	N	QALY
Mueller 2009	Germany	screening	Y	Y	statutory health system	Markov model	lifetime	Y	Y	Y	N	2006 Euro	Y	N	QALY
Berto 2010	Italy	risedronate and alendronate	N	Y	Italian National Healthcare System	Markov state-transition model	6 yrs	Y	N	N	Y	Euro	Y	N	QALY
Borgstrom 2010	UK	strontium ranelate	Y	Y	health care perspective	Markov cohort model	lifetime	Y	Y	Y	Y	2006 Pound	Y	N	QALY
Borgstrom 2010	UK	risedronate	Y	Y	health care perspective	Markov cohort model	lifetime	Y	Y	Y	Y	2006 Pound	Y	N	QALY
Borgstrom 2010	Sweden	parathyroid hormone	Y	Y	societal	Markov model	lifetime	Y	Y	Y	Y	2007 Euro	Y	Y	QALY
Fardellone 2010	France	zoledronic acid, bisphosphonates, raloxifene, strontium ranelate and teriparatide	Y	Y	societal	decision tree model	3 yrs	Y	Y	N	Y	2009 Euro	Y	N	absolute Fx probability

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Study	Country	Assessed intervention	Type of fracture prevention		Evaluation perspective	Type of model	Time horizon	Fracture sites				Costs unit	Costs		Effectiveness measurement
			P	S				Hip	Vertebral	Wrist	Other		D	I	
Hiligsmann 2010	Belgium	strontium ranelate	Y	Y	Belgian healthcare cost	Markov microsimul-ation model	lifetime	Y	Y	Y	Y	2006 Euro	Y	N	QALY
Hiligsmann 2010	Belgium	strontium ranelate	Y	Y	healthcare	Markov microsimul-ation model	lifetime	Y	Y	Y	Y	2006 Euro	Y	N	QALY
Hiligsmann 2010	Belgium	screen and treat with alendronate	Y	Y	healthcare	Markov microsimul-ation model	lifetime	Y	Y	Y	Y	2006 Euro	Y	N	QALY
Hiligsmann 2010	Belgium	bisphosphonate	Y	Y	payer	Markov microsimul-ation model	lifetime	Y	Y	Y	Y	2006 Euro	Y	N	QALY
Hiligsmann 2010	Belgium	bisphosphonate	Y	Y	healthcare	Markov microsimul-ation model	lifetime	Y	Y	Y	Y	2006 Euro	Y	N	QALY
Hiligsmann 2010	Belgium	denosumab	Y	Y	healthcare	Markov microsimul-ation model	lifetime	Y	Y	Y	N	2009 Euro	Y	N	QALY
Logman 2010	UK	zoledronic acid	Y	Y	National Health Service	Markov model	lifetime	Y	Y	Y	Y	2007 Pound	Y	N	QALY
Strom 2010	Sweden	bazedoxifene	Y	Y	societal	Markov model with tunnel techniques	lifetime	Y	Y	Y	Y	Euro	Y	Y	QALY
Thompson 2010	Germany	risedronate and alendronate	Y	Y	German statutory health insurance	Markov state-transition model	5 yrs	Y	N	N	N	2008 Euro	Y	N	QALY

Appendix 2B.3 Table 1: Overview of studies included

Study	Country	Assessed intervention	Type of fracture prevention		Evaluation perspective	Type of model	Time horizon	Fracture sites				Costs unit	Costs		Effectiveness measurement
			P	S				Hip	Vertebral	Wrist	Other		D	I	
Akehurst 2011	Finland, Norway and the Netherlands	zoledronic acid	N	Y	healthcare	individual simulation model	lifetime	Y	Y	Y	Y	2006 Euro for Finland, 2006 NOK for Norway and 2007 Euro for the Netherlands	Y	N	QALY
Borgstrom 2011	Europe	bazedoxifene	Y	Y	healthcare	Markov cohort simulation model	lifetime	Y	Y	Y	Y	2008 Euro	Y	N	QALY
Cotte 2011	France	bisphosphonates	Y	Y	NA	Markov state-transition model	10 yrs	Y	Y	Y	N	2010 Euro	Y	N	Fx occurred
Gauthier 2011	UK	no intervention	Y	Y	no perspective	Markov model	50 yrs	Y	Y	N	Y	NA	Y	N	Fx occurred
Hiligsmann 2011	Belgium	denosumab	Y	Y	healthcare	Markov microsimul-ation model	lifetime	Y	Y	Y	Y	2009 Euro	Y	N	QALY
Jonsson 2011	Sweden	denosumab	Y	Y	societal	Markov cohort model	lifetime	Y	Y	Y	Y	2008 Euro	Y	N	QALY
Majumdar 2011	Canada	multifaceted intervention	N	Y	healthcare	Markov decision-analytic model	lifetime	Y	Y	Y	N	2006 CAD	Y	N	QALY

Appendix 2B.3 Table 1: Overview of studies included

Study	Country	Assessed intervention	Type of fracture prevention		Evaluation perspective	Type of model	Time horizon	Fracture sites				Costs unit	Costs		Effectiveness measurement
			P	S				Hip	Vertebral	Wrist	Other		D	I	
McLellan 2011	UK	Fracture liaison services	N	Y	National Health Service	Markov cohort model	lifetime	Y	N	Y	Y	2009 Pound	Y	N	QALY
Mueller 2011	Germany	diagnosis of osteoporosis and treat with alendronate	Y	Y	German statutory health insurance	Markov model	lifetime	Y	Y	Y	N	2010 Euro	Y	N	QALY
Nayak 2011	USA	screening	Y	Y	payer	Individual state transition model	lifetime	Y	Y	Y	N	2010 USD	Y	N	QALY
Pham 2011	USA	bisphosphonate	Y	Y	societal	Markov model	lifetime	Y	Y	N	Y	2008 USD	Y	Y	QALY
Chau 2012	Canada	denosumab, alendronate, raloxifene, risedronate	Y	Y	payer	Markov model	lifetime	Y	Y	Y	Y	2010 CAD	Y	N	QALY
Cooper 2012	Australia	Minimal Trauma Fracture Liaison	N	Y	universal health care insurance	Markov model	10 yrs	Y	N	Y	Y	2010 AUD	Y	N	QALY
Hiligsmann 2012	Ireland	oral bisphosphonate	Y	Y	healthcare	Markov microsimul-ation model (tracker technique was incorporated)	lifetime	Y	Y	Y	N	2008 Euro	Y	N	QALY
Kingkaew 2012	Thailand	screening and treatment	Y	Y	societal	Markov model	lifetime	Y	Y	N	N	2007 THB	Y	N	QALY
Murphy 2012	Sweden	teriparatide,oral bisphosphonate	N	Y	NA	Markov microsimul-ation model	lifetime	Y	Y	Y	N	2011 Euro	Y	N	QALY

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Study	Country	Assessed intervention	Type of fracture prevention		Evaluation perspective	Type of model	Time horizon	Fracture sites				Costs unit	Costs		Effectiveness measurement
			P	S				Hip	Vertebral	Wrist	Other		D	I	
Pueyo 2012	Spain	alendronate	Y	Y	societal	decision analytic model	10 and 20 yrs	Y	N	N	N	2009 Euro	Y	Y	QALY
Alzahouri 2013	France	branded alendronate	Y	Y	French healthcare system	Markov state-transition model	lifetime	Y	N	N	N	2011 Euro	Y	N	QALY
Moriwaki 2013	Japan	alendronate	Y	Y	health care system	Individual state transition model	5 yrs	Y	Y	N	N	2012 USD	Y	N	QALY
Nshimyumu-kiza 2013	Canada	calcium and vitamin D, physical activity, bisphosphonates	Y	Y	Ministry of Health and Public Medical Insurance	individual Markov decision model	lifetime	Y	Y	Y	N	2007-2008 CAD	Y	N	QALY

Abbreviations: P: primary, S: secondary, D: direct, I: indirect, QALY: quality-adjusted life years, QALE: quality-adjusted life expectancy, Fx: fracture, LY: life year, USD: US dollar, SEK: Swedish krona, CAD: Canadian dollar, CHF: Swiss franc, DKK: Danish krona, THB: Thai Baht, NA: not applicable, Y: yes, N: no.

Appendix 2B.3 Table 2: Costs* of fracture in studies included in the systematic review

	First year after fracture				Second year after fracture			
	Hip	Vertebral	Wrist	Others	Hip	Vertebral	Wrist	Others
USA								
Weinstein 1980	NA	NA	NA	NA	NA	NA	NA	NA
Tosteson 1990	18,460-21,792	NA	NA	NA	NA	NA	NA	NA
Weinstein 1990	17,847-21,068	NA	NA	NA	65,357	NA	NA	NA
Tosteson 1990	20,695 (50-59y) 24,435(80-89y)	NA	NA	NA	NA	NA	NA	NA
Chrischilles 1994	NA	NA	NA	NA	NA	NA	NA	NA
Solomon 2000	18,345	NA	NA	1,256	NA	NA	NA	NA
Grima 2002	48,505	2,474	NA	NA	5,042	93	NA	NA
Buckley 2003	NA	1,105	NA	NA	NA	NA	NA	NA
Schousboe 2005	20,737	8,624	4,794	7,155	8,100	NA	NA	NA
Schousboe 2005	20,737	8,624	4,794	7,155	8,100	NA	NA	NA
Schousboe 2005	20,737	8,624	4,794	7,155	8,100	NA	NA	NA
Borgstrom 2006	15,889	NA	NA	NA	81,527	NA	NA	NA
Liu 2006	21,520	8,801	4,778	NA	NA	NA	NA	NA
Mobley 2006	37,324	2,110	NA	NA	5,055	196	NA	NA

Appendix 2B.3 Table 2: Costs of fracture

	First year after fracture				Second year after fracture			
	Hip	Vertebral	Wrist	Others	Hip	Vertebral	Wrist	Others
Pfister 2006	33,329(65-69y)	3,968(65-69y)	NA	6,954(65-69y)	NA	NA	NA	NA
	35,291(70-74y)	3,884(70-74y)		7,118(70-74y)				
	31,973(75-79y)	3,814(75-79y)		7,720(75-79y)				
	31,982(80-84y)	3,630(80-84y)		7,951(80-84y)				
	25,137(85y+)	3,489(85y+)		8,951(85y+)				
Earnshaw 2007	40,232	2,255	2,109	NA	5,556	242	NA	NA
Danese 2009	35,625	9,460	7,356	7,356	35,625	9,460	7,356	7,356
Lekander 2008	15,402	6,300	3,420	NA	NA	0	0	NA
Tosteson 2008	46,177(65-74y)	3,780(65-74y)	NA	NA	5,494	254	NA	NA
	47,397(75-84y)	3,608(75-84y)						
Tosteson 2008	34,379	9,791	4,897	13,220	8,354	NA	NA	NA
Nayak 2011	23,694	9,691	5,262	NA	78,721(60% of hip fx patients ended up with NH)	NA	NA	NA
Pham 2011	26,050	8,008	NA	15,987	9,144	258	NA	0
UK								
Daly 1992	NA	NA	NA	NA	NA	NA	NA	NA
Torgerson 1993	NA	NA	NA	NA	NA	NA	NA	NA
Torgerson 1996	NA	NA	NA	NA	NA	NA	NA	NA
Iglesias 2002	NA	NA	NA	NA	NA	NA	NA	NA

Appendix 2B.3 Table 2: Costs of fracture

	First year after fracture				Second year after fracture			
	Hip	Vertebral	Wrist	Others	Hip	Vertebral	Wrist	Others
Fleurence 2004	25,461	1,005	982	2,809	NA	NA	NA	NA
Kanis 2004	25,082	991	968	2,768	16,165(10% of hip fx ended up with NH)	314	0	NA
Stevenson 2004	25,082	991	968	2,768	43,186 for NH	407	0	NA
Borgstrom 2006	11,128(50-59y)	NA	NA	NA	36,600	NA	NA	NA
	13,536(60-69y)							
	16,498(70-79y)							
	24,690(80-89y)							
	27,628(90y +)							
Stevenson 2007	9,503(50-54y, not NH)	879(50-54y)	662(50-54y)	NA	43,419(50-54y, NH)	409(50-54y)	0	NA
	9,503(60-64y, not NH)	879(60-64y)	662(60-64y)		43,419(60-64y, NH)	409(60-64y)		
	11,954(70-74y, not NH)	993(70-74y)	662(70-74y)		44,668(70-74y, NH)	409(70-74y)		
	15733(80-84y, not NH)	1,071(80-84y)	1,078(80-84y)		46,726(80-84y, NH)	409(80-84y)		
	57,676(50-54y)							
Stevenson 2007	57,676(60-64y, NH)							
	60,084(70-74y, NH)							
	63,858 (80-84y, NH)							
Strom 2007	22,897(50-64y)	3,723(50-64y)	629(50-64y)	NA	3,900	NA	NA	NA
	23,135(65-74y)	3,365(65-74y)	629(65-74y)					

Appendix 2B.3 Table 2: Costs of fracture

	First year after fracture				Second year after fracture			
	Hip	Vertebral	Wrist	Others	Hip	Vertebral	Wrist	Others
van Staa 2007	27,029(75-84y) 28,562(85y +) 9,503(40-69y, not NH) 11,100(70-79y, not NH) 15,733(80y +, not NH) 53,554(40-69y, NH) 55,790(70-79y, not NH) 63,858(80y +, not NH)	2,791(75-84y) 1,342(85y +) 879(40-69y) 922(70-79y) 1,071(80y +)	1,020(75-84y) 3,201(85y +) 1,752(40-79y) 1,752(80y +)	NA	43,419(40-69y, NH) 43,419(70-79y, NH) 46,726(80y +, NH)	409(40-69y) 409(70-79y) 409(80y +)	NA	NA
Kanis 2008	17,868	2,833	875	22,868 for other femoral fx 15,337 for pelvic fx 244 for rib and sternal fx 1,847 for forearm fx 6,417 for leg fx	NA	0	0	NA
Kanis 2008								
Lekander 2008	16,360-27,566	2,095-3,818	1,098	NA	NA	0	0	NA
Borgstrom 2010 by 2	17,868	2,833	875	22,868 for other femoral fx 15,337 for pelvic fx 244 for rib and sternal fx 1,847 for forearm fx	NA	0	0	NA

Appendix 2B.3 Table 2: Costs of fracture

	First year after fracture				Second year after fracture			
	Hip	Vertebral	Wrist	Others	Hip	Vertebral	Wrist	Others
				6,417 for leg fx	NA	NA	NA	NA
Logman 2010	1,824	2,919	902	NA	1,824	2,919	902	NA
Borgstrom 2011	13,374(50-69y)	3,334	1,527	2,240-2,729	2,738(50-59y)	590(50-59y)	NA	NA
	15,594(70-79y)				2,657(60-69y)	518(60-69y)		
	24,631(80y +)				4,168(70-79y)	820(70-79y)		
					6,007(80y +)	1,719(80y +)		
Gauthier 2011	NA	NA	NA	NA	NA	NA	NA	NA
Scandinavia countries								
Jonsson 1995	26,451	2,713	678	NA	33,911 (10% of the hip fx ended in NH)	0	0	NA
Ankjaer-Jensen 1996	11,148	NA	NA	NA	24,375	NA	NA	NA
Willis 2001	15,306-49,495	622	516	NA	486 for healed hip fx	NA	NA	NA
					3,462 for partial healed hip fx 21,241 for permanently disabled hip fx			
Willis 2002	14,464-46,772	NA	NA	NA	3,650	NA	NA	NA
Johnel 2003	24,468	2,163	541	NA	5,542	NA	NA	NA
Borgstrom 2004	NA	4,119	NA	NA	NA	676	NA	NA
Christensen 2005	NA	NA	NA	NA	5,353 for severe hip fx	281	1,907	NA

Appendix 2B.3 Table 2: Costs of fracture

	First year after fracture				Second year after fracture			
	Hip	Vertebral	Wrist	Others	Hip	Vertebral	Wrist	Others
					402 for moderate hip fx			
Zethraeus 2005	8,106	7,863	2,898	NA	9,903 for NH fx	NA	NA	NA
Borgstrom 2006	12,349(50-64y)	4,681	2,974	NA	7,963	0	0	NA
	13,443(65-74y)							
	23,742(75-84y)							
	33,185(85-100y)							
Borgstrom 2006	15,104(50-64y)	NA	NA	NA	81,241 for NH hip fx	NA	NA	NA
Borgstrom 2006	15,465(65-74y)							
	16,142(75-84y)							
	22,179(85y +)							
Borgstrom 2006	10,967(50-64y)	4,157	2,642	2,742	5,013(50-64y)	566	0	0
	11,940(65-74y)				4,903(65-74y)			
	21,086(75-84y)				7,661(75-84y)			
	29,473(85y +)				16,937(85y +)			
Lundkvist 2006	12,284(50-64y)	4,419	2,807	NA	7,272	725	NA	NA
	13,300(65-74y)							
	23,437(75-84y)							
	32,760(85y +)							

Appendix 2B.3 Table 2: Costs of fracture

	First year after fracture				Second year after fracture			
	Hip	Vertebral	Wrist	Others	Hip	Vertebral	Wrist	Others
Strom 2007	12,572(50-64y) 13,685(64-74y) 24,169(75-84y) 33,782(85y +)	4,765	3,028	NA	8,107	NA	NA	NA
Strom 2007	22,968	1,213	883	NA	7,058	NA	NA	NA
Strom 2007	29,282	1,528	1,327	NA	5,369	NA	NA	NA
Lekander 2008	13,526-17,146	2,215-13,685	3,072	NA	based on age specific NH status: 6.7%-22.6%	0	0	NA
Borgstrom 2010	11,790-14,567	3,059-9,677	2,752	8,307	3,934-16,889 for NH hip fx 153-3,776 for hip fx	1,629-5,951	0	0
Strom 2010	13,521-24,901	2,333-16,194	2,864	4,571-11,709	5,256-11,532	637-1,856	264	0
Akehurst 2011	11,025	1,398	1,199-2,629	1,320-2,295	53,788	461	NA	NA
Akehurst 2011	14,557	2,512	2,061	2,061	70,202	NA	NA	NA
Borgstrom 2011	13,521(50-64y) 16,405(65-74y) 17,121(75-84y) 24,901(85y +)	2,333(50-59y) 15,878(60-69y) 16,437(70-79y) 16,194(80y +)	2,864	4571-11709	5,256(50-59y) 5,211(60-69y) 8,177(70-79y) 11,532(80y +)	637(50-59y) 572(60-69y) 904(70-79y) 1,856(80y +)	264	0
Jonsson 2011	15,780(50-64y) 16,262(65-74y)	2,511(50-64y) 16,729(65-74y)	2,944	5,076(50-54y) 5,471(55-59y)	NA	0	0	0

Appendix 2B.3 Table 2: Costs of fracture

	First year after fracture				Second year after fracture			
	Hip	Vertebral	Wrist	Others	Hip	Vertebral	Wrist	Others
Jonsson 2011	18,151(75-84y) 24,114(85y +)	17,317(75-84y) 17,434(85y +)		6,513(60-64y) 10,840(65-69y) 11,110(70-74y) 10,489(75-79y) 9,880(80-84y) 10,713(85y +)				
Murphy 2012	11,389(50-64y) 12,694(65-74y) 22,369(75-84y) 30,373(85y +)	4,097	2,603	NA	6,742	672	NA	NA
Belgium								
Strom 2007	22,107	4,990	1,350	NA	2,677	NA	NA	NA
Hiligsmann 2008	21,500-27,432	3,173	2,821	4,668	1,295-5,977	NA	NA	NA
Hiligsmann 2009	21,500-27,433	3,173	2,821	4,668	25,895-19,919 for NH	NA	NA	NA
Hiligsmann 2010 by 6	21,500-27,433	3,173	2,821	4,668	25,895-19,919 for NH	NA	NA	NA
Canada								
Rosner 1998	NA	2,190	NA	NA	NA	NA	NA	NA
Singh 2004	17,397 for acute hospital treatment	NA	NA	NA	NA	NA	NA	NA

Appendix 2B.3 Table 2: Costs of fracture

	First year after fracture				Second year after fracture			
	Hip	Vertebral	Wrist	Others	Hip	Vertebral	Wrist	Others
	119,907 for NH							
Grima 2008	23,207	NA	NA	NA	4,973(65-74y)	NA	NA	NA
					2,614(75-84y)			
					0(85y +)			
Majumdar 2009	NA	NA	NA	NA	NA	NA	NA	NA
Majumdar 2011	27,549	1,893	1,359	NA	44,107 for NH hip fx (20%)	NA	NA	NA
Chau 2012	16,560(50-59y)	8,642(50-59y)	1,174(50-59y)	NA	3,886	177	NA	NA
	15,786(60-69y)	11,602(60-69y)	1,664(60-69y)					
	20,805(70-79y)	14,066(70-79y)	4,288(70-79y)					
	22,522(80-89y)	17,910(80-89y)	10,716(80-89y)					
	20,719(90y +)	21,432(90y +)	14,716(90y +)					
Nshimyumukiza 2013	20,980	NA	NA	NA	NA	NA	NA	NA
Germany								
Brecht 2003	23,943	6,958(50-64y)	NA	NA	11,851	NA	NA	NA
		7,637(65-74y)						
		8,528(75-100y)						
Brecht 2004	13,265 for SHI	7,037 for SHI	NA	NA	NA	NA	NA	NA
Brecht 2004	9,504 for LTCI							

Appendix 2B.3 Table 2: Costs of fracture

	First year after fracture				Second year after fracture			
	Hip	Vertebral	Wrist	Others	Hip	Vertebral	Wrist	Others
	22,768 for SHI							
Borgstrom 2006	20,987	NA	NA	NA	62,349	NA	NA	NA
Strom 2007	22,864	6,644(50-64y)	1,396	NA	4,050	NA	NA	NA
		7,292(65-74y)						
		8,144(75-84y)						
		8,144(85y +)						
Kreck 2008	18,194(40-49y)	4,262(40-49y)	4,524(40-49y)	NA	7,075(65y +)	NA	NA	NA
	18,218(50-59y)	4,279(50-59y)	4,524(50-59y)					
	18,476(60-64y)	4,306(60-64y)	4,524(60-64y)					
	21,467(65-69y)	2,848(65-69y)	959(65-69y)					
	21,624(70-79y)	2,902(70-79y)	1,012(70-79y)					
	21,955(80-89y)	2,848(80-89y)	959(80-89y)					
Mueller 2008 by 3	NA	5,602	5,373	NA	NA	NA	NA	NA
Thompson 2010	31,303	NA	NA	NA	15,495	NA	NA	NA
Borgstrom 2011	24,099	7,003(50-64y)	1,471	NA	2,904(50-59y)	537(50-59y)	NA	NA
		7,687(65-74y)			2,817(60-69y)	472(60-69y)		
		8,583(75y +)			4,352(70-79y)	748(70-79y)		
					7,007(80y +)	1,566(80y +)		

Appendix 2B.3 Table 2: Costs of fracture

	First year after fracture				Second year after fracture			
	Hip	Vertebral	Wrist	Others	Hip	Vertebral	Wrist	Others
Mueller 2011	40,625-86,281	5,344	5,126	NA	NA	NA	NA	NA
Japan								
Nagata-Kobayashi 2002	18,462	NA	NA	NA	5,539-21,819	NA	NA	NA
Borgstrom 2006	28,016	NA	NA	NA	44,682	NA	NA	NA
Ding 2008	NA	NA	NA	NA	NA	NA	NA	NA
Moriwaki 2013	27,967	9,829	NA	NA	44,339 for nursing home fx which took 13.6% of all hip fx	NA	NA	NA
Australia								
Cheung 1992	10,232	584	NA	NA	NA	NA	NA	NA
Geelhoed 1994	8,357	584	NA	NA	NA	NA	NA	NA
Borgstrom 2006	14,213	NA	NA	NA	35,746	NA	NA	NA
Cooper 2012	14,630	NA	1,671	3,736	2,994	NA	NA	NA
Switzerland								
Sendi 2000	NA	NA	NA	NA	NA	NA	NA	NA
Schwenkglenks 2007	NA	NA	NA	NA	4,227	1,476	1,148	NA
Wasserfallen 2008	33,484(50-64y)	25,887(50-64y)	9,157(50-64y)	NA	2,131(50-64y, NH)	NA	NA	NA
	52,701(65-74y)	26,385(65-74y)	10,148(65-74y)		4,363(65-74y, NH)			

Appendix 2B.3 Table 2: Costs of fracture

	First year after fracture				Second year after fracture			
	Hip	Vertebral	Wrist	Others	Hip	Vertebral	Wrist	Others
	57,740(75-84y)	27,399(75-84y)	13,856(75-84y)		6,659(75-84y, NH)			
	56,488(85y +)	47,905(85y +)	33,296(85y +)		9,142(85y +, NH)			
Thailand								
Panichkul 2006	1,698	NA	NA	NA	NA	NA	NA	NA
Kingkaew 2012	5,391	5,157	NA	NA	NA	NA	NA	NA
Spain								
Borgstrom 2006	8,882	2,769	543	NA	2,042	NA	NA	NA
Borgstrom 2006	10,123	NA	NA	NA	41,433	NA	NA	NA
Borgstrom 2011	16,351	3,617	998	1,687-2,057	4,367(50-59y)	444(50-59y)	NA	NA
					4,237(60-69y)	391(60-69y)		
Borgstrom 2011					6,648(70-79y)	618(70-79y)		
					9,581(80y +)	1,295(80y +)		
Strom 2007	9,096	2,012	556	NA	2,091	NA	NA	NA
Pueyo 2012	15,820	NA	NA	NA	10,616	NA	NA	NA
France								
Schott 2007	23,680	NA	NA	NA	NA	NA	NA	NA
Strom 2007	11,728(50-64y)	4,446	2,825	NA	7,563	NA	NA	NA
	12,768(65-74y)							

Appendix 2B.3 Table 2: Costs of fracture

	First year after fracture				Second year after fracture			
	Hip	Vertebral	Wrist	Others	Hip	Vertebral	Wrist	Others
	22,548(75-84y)							
	31,516(85y +)							
Fardellone 2010	10,136-10,991	upper limit of 7,743	NA	2,971	NA	NA	NA	NA
Borgstrom 2011	12,916(50-69y)	3,221	1,475	NA	2,645(50-59y)	569(50-59y)	NA	NA
	15,055(70-79y)				2,566(60-69y)	500(60-69y)		
	23,788(80y +)				4,026(70-79y)	792(70-79y)		
					5,802(80y +)	1,661(80y +)		
Alzahouri 2013	17,520	NA	NA	NA	24,873 for NH hip fx	NA	NA	NA
Italy								
Strom 2007	22,968	5,080	1,402	NA	2,741	NA	NA	NA
Berto 2010	14,421	NA	NA	NA	1,645	NA	NA	NA
Borgstrom 2011	24,378	5,392	1,489	NA	4,186(50-59y)	662(50-59y)	NA	NA
					4,061(60-69y)	583(60-69y)		
					6,373(70-79y)	922(70-79y)		
					9,581(80y +)	1,931(80y +)		
The Netherlands								
Jansen 2008	82,025 (NH)	699	1,189	1,459	60754 (NH)	139	63	177
Akehurst 2010	20,478	9,938	1,371	1,371	41,565	NA	NA	NA

Appendix 2B.3 Table 2: Costs of fracture

	First year after fracture				Second year after fracture			
	Hip	Vertebral	Wrist	Others	Hip	Vertebral	Wrist	Others
Ireland								
Hiligsmann 2012	14,282-16,734	2,483-2,910	NA	NA	5,666-6,119	NA	NA	NA
	15,350-17,883	2,669-3,110	NA	NA	5,760-6,170	NA	NA	NA

Abbreviations: NA: not applicable, fx: fracture, NH: nursing home dwelling, SHI: Social Health Insurance, LTCI: statutory long-term care insurance.

* Costs data were converted into 2013 US dollars using a web-based currency convertor.

Chapter 3: A systematic review and meta-analysis of utility-based quality of life for osteoporosis-related conditions

3.1 Preface

This chapter provides a systematic review and meta-analysis of health-state utility values for osteoporosis-related conditions. This study statistically combines multiple health state utility values (HSUVs) reported in the literature for patients with osteoporosis and osteoporotic fractures. Fracture events are associated with decrements in HSUVs which differed between fracture sites and time since the occurrence of fractures. In addition, we have provided summary values for use in future health economics analyses in osteoporosis, that we later implemented in the health economics model described in Chapter 4.

This chapter has been published in *Osteoporosis International* (Appendix 3A).

Impact factor: 4.17.

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The published article of this chapter appears in an appendix to the chapter. It has been removed for copyright or proprietary reasons.

3.2 Abstract

Introduction: Osteoporotic fractures have high financial and health burden. Economic evaluations on osteoporotic fracture prevention have been frequently performed in past decades. One of the challenges in the economic evaluations was to identify consistent health state utility values (HSUVs) to use for osteoporotic fracture related conditions. The objective of this study was to determine summary measures of multiple HSUVs reported in the literature for patients with osteoporosis and osteoporotic fractures.

Methods: We performed a systematic review, meta-analysis and meta-regression of published literature that reported HSUVs for osteoporotic fracture related conditions.

Results: There were 62 studies representing 142,477 patients included. In total, 362 HSUVs were identified: 106 for pre-fracture; 89 for post-hip fracture; 130 for post-vertebral fracture and 37 for post-wrist fracture. The pooled HSUVs, using a random-effects model were 0.76 (95% CI: 0.75, 0.77, I^2=0.99) for pre-fracture; 0.57 (95% CI: 0.52, 0.63, I^2=1) for post-hip fracture; 0.59 (95% CI: 0.55, 0.62, I^2=0.99) for post-vertebral facture and 0.72 (95% CI: 0.67, 0.78, I^2=1) for post-wrist fracture. Heterogeneities were addressed through meta-regression. HSUVs immediately following hip, vertebral and wrist fracture were 0.31, 0.44 and 0.61 respectively. Patients' HSUVs improved over time following fracture events: HSUVs for the first year after hip, vertebral and wrist fracture were 0.59, 0.55 and 0.78 respectively; and 0.66, 0.66 and 0.81 for subsequent years.

Conclusions: Fractures were associated with significant decrements in HSUVs. This study provides a standard set of HSUVs that can be used in health economic assessments in osteoporosis.

3.3 Introduction

Osteoporosis is characterized by reduced bone mass and disruption of bone structure, resulting in increased risk of fracture and bone fragility [1]. It was estimated 200 million women were affected by osteoporosis and about 9 million fractures occurred globally in 2000 [2]. Though a downward trend in fracture rates was observed in the past decade regionally [3], a recent report suggested the number of men and women with osteoporosis is expected to rise from 27.5 million in 2010 to 33.9 million in 2025 across European countries [4].

Increase in health care expenditure for osteoporosis is driven by the costs of pharmaceutical medicines, making up 70% of the total costs [3]. Cost-effectiveness analysis models that assess whether medications/interventions provide good value for money, have been increasingly used in past decades [5-8]. One of the challenges for modelling osteoporosis interventions is estimating a health state utility value (HSUV) to calculate the quality adjusted life years (QALYs) [9], because the HSUVs used in decision analytic models can have a substantial impact on the cost-effectiveness of the assessed invention [10].

HSUVs are cardinal values to measure patients' health preferences, generally ranging between 0 and 1, where 1 represents perfect health, 0 represents death, and can be derived from direct measurements such as standard gamble (SG), rating scale and time trade off (TTO) [11], or alternatively from multi-attribute health state descriptive systems such as EQ-5D, Quality of Well Being (QWB) [12], Health Utilities Index (HUI) [13], and SF-6D [14]. Particularly, EQ-5D HSUV was recommended by National Health Institute for Clinical Excellence (NICE) [15] and was substantially used in evaluating HSUVs in osteoporosis context [16-18]. The EQ-5D evaluates the health status through 243 distinct health states across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) [19], from which HSUVs can be derived based on different population norms.

Evidence on osteoporotic fracture conditions have been previously discussed: Brazier et al. [20] and Peasgood et al. [16] conducted systematic reviews up to 2007, providing estimated HSUV multipliers based on empirical evidences for osteoporotic fractures. However, there were some discrepancies between the two studies: Peasgood's estimates for hip fractures and vertebral fractures were considerably lower than that in Brazier's review [16, 20]. Furthermore, neither of the previous reviews provided the HSUVs for subsequent year after

vertebral and wrist fracture because of limited evidence [16]. The aims of this review were two-fold: 1) provide summary measures of HSUVs for osteoporosis related conditions, including HSUVs for pre-fracture, post-hip, post-vertebral and post-wrist fractures, accounting for important parameters like time after fracture, age and sex; and 2) provide HSUVs prediction algorithms through meta-regression analyses.

3.4 Methods

3.4.1 Literature search

This systematic review was conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. A systematic search was performed in broad electronic database searches including 2 biomedical databases, 3 health economics databases, Wiley library database and Cochrane database. Biomedical databases were MEDLINE and Embase. Health economics databases were searched in NHS Economic Evaluation Database (NHS EED), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database (HTA).

3.4.2 Search methods

Both thesaurus and free-text term searches were performed to identify possible studies. The search strategy (Appendix 3B.1) was based on that developed by Brazier and colleagues [22]. The sensitive search terms ensured the search returned a wide range of potential studies. Furthermore, the references of the retrieved studies were hand-searched to identify any studies missed by electronic database searches.

3.4.3 Study selection

The search was performed without limitations to year of publication. Studies reporting osteoporosis or osteoporotic fracture-related HSUVs were included in our review. We included studies in languages other than English if there were sufficient data for meta-analyses. Abstracts and working papers were also included. Health economic modelling studies using secondary HSUV data, i.e. HSUV that had already been reported originally from trials, were excluded in our study. Studies that did not provide sufficient data for meta-analyses were also excluded. Studies reporting quality of life scores without reporting HSUVs, or where HSUVs could not be generated by mapping functions, were excluded. In addition, systematic reviews or meta-analyses were excluded.

3.4.4 Data extraction and management

Study characteristics and data for meta-analyses were retrieved onto standardized data sheets by 2 independent reviewers. Any disagreement was resolved through discussion. The reviewers were not blinded to study authors, affiliations, or journal names [23]. Data extracted were authors and year of publication, country, number of patients, utility elicitation method, mean age, proportion of females and HSUV estimates. Pre-fracture HSUVs referred to HSUVs from osteoporosis patients without a fracture or retrospectively from patients with fractures evaluating the HSUV for the condition prior to the fracture event. Pre-fracture HSUV type was defined in terms of whether the HSUV was retrospective, i.e. recall HSUV collected after the fracture event. Additionally, time after fracture and whether the patients had fracture history were extracted for post-fracture conditions.

3.4.5 Data analysis

The HSUVs were pooled through meta-analyses, using random-effects models that accounted for both within-trial variance and between-trial heterogeneity [24]. Heterogeneity was assessed by I^2 statistic in Cochran's Q tests [25] which quantifies inconsistency across studies and describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error (chance) [26]. HSUVs were weighted by the inverse of variance [27]. Where studies did not report standard deviations, missing data were calculated, where possible, using standard error and number of patients [28]. For studies that did not provide either the variance or standard error, the standard error was imputed from other studies that provided a standard deviation, using multiple imputation [29]. The number of iterations was the proportion of missing data [30].

Significance of subgroups was determined by Wald test [31]. We performed subgroup analyses by age, sex, HSUV elicitation method and type, fracture history and country for pre-fracture condition. For post-fracture condition, factors such as time after fracture, age, sex, fracture history and country were included in subgroup analyses to determine whether the HSUVs varied by the chosen factors. Point and interval HSUV estimates for the sum of coefficients were determined using linear combinations of coefficients [32]. The HSUV prediction model was provided using multi-variable meta-regression adjusted for covariates [33]. All statistical analyses were performed using STATA (STATA12.1, StataCorp LP, College Station, TX, USA) and statistical significance was set as a *p*-value equal to or less than 0.05 (two-tailed).

3.5 Results

3.5.1 Study characteristics

The flow chart for identifying included studies is given in *Figure 3.1*. Initially, the electronic database searches identified 9,077 tittles after duplicates were removed. There were 362 articles and abstracts remaining after title screening. After screening by abstract and full text, 56 articles remained. Six additional studies were identified from reference lists of retrieved publications.

Finally, there were 62 studies included (Appendix 3B.2), representing 142,477 patients. A total of 362 HSUVs were identified from the included studies: 106 for pre-fracture, 89 for post-hip fractures, 130 for post-vertebral fracture and 37 for post-wrist fracture. A summary of characteristics of included studies is given in Appendix 3B.3. Most of the studies used EQ-5D HSUVs, followed by visual analogue scale (VAS) and only a small number of studies used direct measurements. Study characteristics for pre-fracture, post-hip fracture, post-vertebral fracture and post-wrist fracture are given in *Appendix 3B.4 Table 1, 2, 3 and 4* respectively.

3.5.2 Imputation of standard deviations

For the pre-fracture condition, standard deviations were available for 93 (88%) HSUVs (of 106). The standard deviation imputations ranged from 0.10 to 0.21. For post-hip fracture, standard deviations were available for 78 (88%) HSUVs (of 89) and the imputations for missing standard deviation ranged from 0.17 to 0.26. For post-vertebral fracture, standard deviations were available for 79 (61%) (of 130) and the imputations ranged from 0.18 to 0.31. Imputation was not performed for post-wrist fracture HSUVs since there were no missing standard deviation data.

3.5.3 Pooled HSUV estimates

The pooled HSUV for the pre-fracture condition was estimated to be 0.76 (95% CI: 0.75, 0.77), the I^2 statistic in Cochran's Q test was 0.99. For post-hip fracture, the HSUV estimate was 0.57 (95% CI: 0.52, 0.63, I^2=1). For post-vertebral fracture, the HSUV estimate was 0.59 (95% CI: 0.55, 0.62, I^2=0.99). The pooled HSUV for post-wrist fracture was 0.72 (95% CI: 0.67, 0.78, I^2=1).

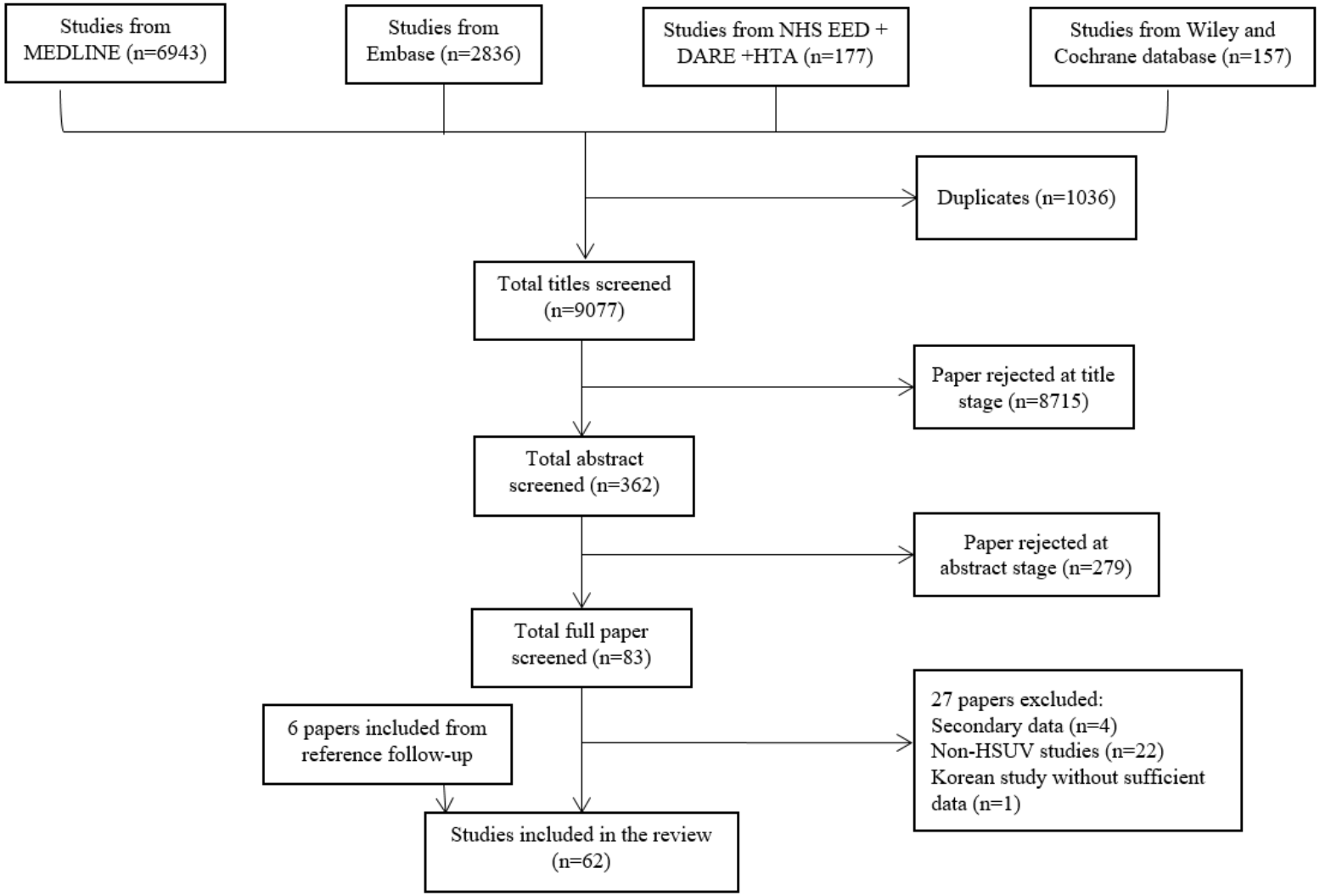

Figure 3.1 Flow diagram for study selection

3.5.4 Subgroup analyses

Pre-fracture

The country from which HSUVs were retrieved was found to have no influence on HSUVs using Wald test (p=0.80). Similarly, patients' sex and fracture history were found to have no significant impact on HSUVs (p=0.11 and p=0.87 respectively) (*Table 3.1*).

Table 3.1 Pre-fracture HSUVs meta-regressions

Analysis	Factor	Coefficient estimates ** (95% CI)	*p*-value	HSUV estimates (95% CI)
Age group (subgroup difference *p*=0.02*)	Intercept	0.84 (0.76, 0.92)	<0.001	
	<60	*ref.*		0.84 (0.76, 0.92)
	60-69	-0.07 (-0.15, -0.02)	0.14	0.78 (0.74, 0.81)
	70-79	-0.11 (-0.19, -0.02)	0.02	0.74 (0.70, 0.78)
	≥80	-0.11 (-0.21, -0.02)	0.02	0.73 (0.67, 0.78)
HSUV elicitation method (subgroup difference *p*<0.001*)	Intercept	0.78 (0.75, 0.80)	<0.001	
	EQ-5D	*ref.*		0.78 (0.75, 0.80)
	HUI	-0.01 (-0.12, 0.10)	0.89	0.77 (0.66, 0.88)
	Rating scale	0.12 (-0.15, 0.26)	0.09	0.90 (0.76, 1.00)
	SF-36	-0.06 (-0.24, 0.13)	0.56	0.72 (0.53, 0.91)
	SG	0.14 (0.00, 0.28)	0.05	0.92 (0.78, 1.00)
	TTO	-0.08 (-0.16, 0.01)	0.42	0.71 (0.62, 0.79)
	VAS	-0.13 (-0.18, -0.08)	<0.001	0.65 (0.60, 0.70)
HSUV type (subgroup difference *p*=0.02*)	Intercept	0.73 (0.71, 0.76)	<0.001	
	Not retrospective	*ref.*		0.73 (0.71, 0.76)
	Retrospective	0.05 (0.01, 0.09)	0.01	0.78 (0.76, 0.82)
Country (subgroup difference *p*=0.80*)	Intercept	0.75 (0.69, 0.81)	<0.001	
	Asian	*ref.*		0.75 (0.69, 0.81)
	Not Asian	0.01(-0.06, 0.07)	0.79	0.75 (0.73, 0.78)
Patients' sex (subgroup difference *p*=0.11*)	Intercept	0.74 (0.71, 0.77)	<0.001	
	Female	*ref.*		0.74 (0.71, 0.77)
	Mixed	0.03(-0.01, 0.07)	0.14	0.77 (0.74, 0.80)
Fracture history (subgroup difference *p*=0.87*)	Intercept	0.72 (0.53, 0.90)	<0.001	
	Not fractured	*ref.*		0.72 (0.53, 0.90)
	Mixed	0.01(-0.28, 0.29)	0.96	0.72 (0.50, 0.94)

HSUV, Health state utility value, HUI, Health utility index, SG, Standard gamble, TTO, Time trade-off, VAS, Visual analogue scale.

*Significance of subgroup was determined by Wald test.

** Mean difference from the reference value.

Mean patient age was a significant predictor of HSUVs: patients aged less than 60 years had a HSUV of 0.84 (95% CI: 0.76, 0.92), and HSUVs for patients aged 60 to 69 years, 70 to 79 years and older than 80 years, were all lower than that of the reference group (differences were -0.07, -0.11 and -0.11 respectively).

The HSUV elicited from the EQ-5D using population norm was 0.78 (95% CI: 0.75, 0.80). HSUVs derived from the EQ-5D VAS were significantly lower than that of the reference group: the difference was -0.13. The retrospective HSUVs were significantly higher than that of non-retrospective: the difference was 0.05.

Post-hip fracture

Time after fracture influenced HSUV for post-hip fracture condition ($p<0.001$): HSUV immediately after a fracture was estimated to be 0.31 (95% CI: 0.22, 0.39). HSUVs for 1 year and subsequent years after fracture were higher than that of the reference group: the differences were 0.29 and 0.35 respectively. Patients' sex and whether the study was of patients with prevalent fractures also affected HSUVs ($p=0.04$ and $p<0.001$ respectively): HSUVs from a mixed population were 0.11 ($p=0.04$) lower than the female population. A population with prevalent fractures had a HSUV 0.31 lower than that of the population free from fracture history ($p<0.001$).

HSUVs elicitation methods ($p=0.10$) may potentially influence HSUVs. EQ-5D VAS and standard gamble HSUVs were higher than the EQ-5D HSUVs generated from population norms, the differences were 0.15 and 0.36 respectively.

Age group and country, however, were found to have no influence on HSUVs ($p=0.32$ and $p=0.11$ respectively) (*Table 3.2*).

Post-vertebral fracture

Time after fracture, patient age and patients' sex influenced the HSUVs for the post-vertebral fracture condition ($p<0.001$, $p=0.01$ and $p=0.001$ respectively): The HSUV for immediately after vertebral fracture was 0.44 (95% CI: 0.37, 0.51), and HSUVs for the first year and subsequent years were 0.11 and 0.22 higher respectively than that of the reference group. The patients aged less than 70 years had higher HSUVs than patients aged 70 to 75 years and patients aged above 75 years, with differences of -0.14 and -0.13 respectively. The female population had a HSUV of 0.69 (95% CI: 0.63, 0.74), which was 0.15 higher than that of the mixed gender population.

Country and fracture history had no impact on HSUVs (p=0.54 and p=0.10). Utility elicitation methods may potentially affect HSUV (p=0.11), this factor was also included in subgroup analysis (*Table 3.3*).

Post-wrist fracture

Time after fracture, patients' sex and fracture history affected the HSUVs for post-wrist fracture condition (p=0.001, p=0.03 and p=0.02 respectively): HSUV for immediately after fracture was 0.61 (95% CI: 0.54, 0.67), and HSUVs for first year and subsequent years were higher than that of the reference group: the differences were 0.17 and 0.20 respectively. The mixed population group had a lower HSUV than the female population, with a HSUV difference of -0.13. Patients with prevalent fractures were also found to have lower HSUVs compared with patients free from fractures (the difference was -0.13).

HSUV elicitation method and patient age however had no influence on HSUVs (p=0.22 and p=0.97) (*Table 3.4*).

3.5.5 HSUVs prediction models

HSUV prediction models were given for pre-fracture, post-hip fracture, post-vertebral fracture and post-wrist fracture (*Table 3.5*) using multivariable meta-regressions. Covariates used in pre-fracture models were patients' age, HSUV elicitation methods and HSUV types. Covariates used in post-fracture models were time after fracture, patients' age, HSUV elicitation method, patients' sex and fracture history. The explanatory powers R^2 for pre-fracture, post-hip, post-vertebral and post-wrist fracture models were 0.31, 0.63, 0.45 and 0.56 respectively.

Patients' age, sex, fracture history, HSUV elicitation method and whether the HSUVs were retrospective did not explain heterogeneity seen between studies for all pre- and post-fracture HSUVs. Additionally, time after fracture did not explain heterogeneity for post-fracture HSUV studies. Residual heterogeneities remained high for all conditions (pre-fracture: I^2=0.99, post-hip fracture: I^2=0.98, post-vertebral fracture: I^2=0.98, post-wrist fracture: I^2=0.99).

Table 3.2 Post-hip fracture HSUVs meta-regressions

Analysis	Factor	Coefficient estimates ** (95% CI)	*p*-value	HSUV estimates (95% CI)
Time after fracture (subgroup difference *p*<0.001*)	Intercept	0.31 (0.22, 0.39)	<0.001	
	Immediate	*ref.*		0.31 (0.22, 0.39)
	First year	0.29 (0.19, 0.39)	<0.001	0.59 (0.54, 0.65)
	Subsequent years	0.35 (0.25, 0.44)	<0.001	0.65 (0.60, 0.70)
Sex (subgroup difference *p*=0.04*)	Intercept	0.66 (0.57, 0.76)	<0.001	
	Female	*ref.*		0.66 (0.57, 0.76)
	Mixed	-0.11 (-0.22, -0.01)	0.04	0.55 (0.51, 0.60)
Fracture history (subgroup difference *p*=0.001*)	Intercept	0.64 (0.61, 0.68)	<0.001	
	Not fractured	*ref.*		0.64 (0.61, 0.68)
	Mixed	-0.31 (-0.39, -0.23)	<0.001	0.34 (0.27, 0.40)
HSUV elicitation method (subgroup difference *p*=0.10*)	Intercept	0.51 (0.47, 0.56)	<0.001	
	EQ-5D	*ref.*		0.51 (0.47, 0.56)
	HUI	0.17 (-0.04, 0.40)	0.12	0.69 (0.47, 0.90)
	QWB	0.10 (-0.27, 0.46)	0.61	0.61 (0.24, 0.98)
	SG	0.36 (0.09, 0.63)	0.01	0.88 (0.61, 1.00)
	TTO	0.15 (-0.09, 0.38)	0.22	0.66 (0.43, 0.89)
	Rating scale	0.22 (-0.05, 0.49)	0.11	0.73 (0.47, 1.00)
	VAS	0.15 (0.06, 0.25)	0.002	0.67 (0.58, 0.75)
Age group (subgroup difference *p*=0.32*)	Intercept	0.50 (0.35, 0.64)	<0.001	
	<70	*ref.*		0.50 (0.35, 0.64)
	70-74	0.14(-0.03, 0.30)	0.1	0.64 (0.56, 0.71)
	75-79	0.07(-0.09, 0.23)	0.38	0.57 (0.51, 0.63)
	≥80	0.02(-0.16, 0.20)	0.81	0.52 (0.42, 0.62)
Country (subgroup difference *p*=0.11*)	Intercept	0.73 (0.53, 0.92)	<0.001	
	Asian	*ref.*		0.73 (0.53, 0.92)
	Not Asian	-0.16(-0.36, 0.04)	0.13	0.57 (0.52, 0.61)

HSUV, Health state utility value, HUI, Health utility index, QWB, Quality of well-being, SG, Standard gamble, TTO, Time trade-off, VAS, Visual analogue scale.

*Significance of subgroup was determined by Wald test. ** Mean difference from the reference value.

Table 3.3 Post-vertebral fracture HSUVs meta-regressions

Analysis	Factor	Coefficient estimates ** (95% CI)	*p*-value	HSUV estimates (95% CI)
Time after fracture (subgroup difference *p*<0.001*)	Intercept	0.44 (0.37, 0.51)	<0.001	
	Immediate	*ref.*		0.44 (0.37, 0.51)
	First year	0.11 (0.03, 0.20)	0.01	0.55 (0.50, 0.60)
	Subsequent years	0.22 (0.14, 0.31)	<0.001	0.66 (0.62, 0.71)
Age (subgroup difference *p*=0.01*)	Intercept	0.69 (0.63, 0.76)	<0.001	
	<70	*ref.*		0.69 (0.63, 0.76)
	70-74	-0.14 (-0.23, -0.06)	<0.001	0.55 (0.50, 0.60)
	≥75	-0.13 (-0.21, -0.04)	<0.001	0.56 (0.51, 0.61)
HSUV elicitation method (subgroup difference *p*=0.11*)	Intercept	0.56 (0.53, 0.60)	<0.001	
	EQ-5D	*ref.*		0.56 (0.53, 0.60)
	HUI	0.22 (0.01, 0.43)	0.04	0.78 (0.57, 0.99)
	QWB	0.09 (-0.17, 0.34)	0.5	0.65 (0.40, 0.90)
	SG	0.31 (0.05, 0.57)	0.02	0.88 (0.62, 1.00)
	TTO	0.14 (-0.01, 0.30)	0.07	0.71 (0.56, 0.86)
	Rating scale	0.23 (-0.02, 0.49)	0.08	0.80 (0.54, 1.00)
	VAS	0.01 (-0.07, 0.10)	0.74	0.58 (0.50, 0.65)
Sex (subgroup difference *p*=0.04*)	Intercept	0.69 (0.63, 0.74)	<0.001	
	Female	*ref.*		0.69 (0.63, 0.74)
	Mixed	-0.15 (-0.21, -0.08)	<0.001	0.54 (0.50, 0.58)
Country (subgroup difference *p*=0.54*)	Intercept	0.73 (0.53, 0.92)	<0.001	
	Asian	*ref.*		0.73 (0.53, 0.92)
	Not Asian	-0.16(-0.36, 0.04)	0.13	0.58 (0.55, 0.62)
Fracture history (subgroup difference *p*=0.10*)	Intercept	0.64 (0.61, 0.68)	<0.001	
	Not fractured	*ref.*		0.64 (0.61, 0.68)
	Mixed	-0.06 (-0.12, 0.01)	0.09	0.56 (0.51, 0.60)

HSUV, Health state utility value, HUI, Health utility index, QWB, Quality of well-being, SG, Standard gamble, TTO, Time trade-off, VAS, Visual analogue scale.

*Significance of subgroup was determined by Wald test.

** Mean difference from the reference value.

Table 3.4 Post-wrist fracture HSUVs meta-regressions

Analysis	Factor	Coefficient estimates ** (95% CI)	*p*-value	HSUV estimates (95% CI)
Time after fracture (subgroup difference *p*=0.001)	Intercept	0.61 (0.54, 0.67)	<0.001	
	Immediate	*ref.*		0.61 (0.54, 0.67)
	First year	0.17 (0.08, 0.26)	<0.001	0.78 (0.72, 0.84)
	Subsequent years	0.20 (0.08, 0.33)	<0.001	0.81 (0.70, 0.92)
HSUV elicitation method (subgroup difference *p*=0.22*)	Intercept	0.70 (0.65, 0.75)	<0.001	
	EQ-5D	*ref.*		0.70 (0.65, 0.75)
	HUI	0.16 (-0.05, 0.37)	0.13	0.86 (0.66, 1.00)
	SG	0.17 (-0.05, 0.40)	0.13	0.87 (0.65, 1.00)
	Rating scale	0.14 (-0.07, 0.36)	0.9	0.84 (0.63, 1.00)
	VAS	0.02 (-0.28, 0.31)	0.19	0.72 (0.43, 1.00)
Sex (subgroup difference *p*=0.03*)	Intercept	0.81 (0.73, 0.90)	<0.001	
	Female	*ref.*		0.81 (0.73, 0.90)
	Mixed	-0.13 (-0.23, -0.03)	0.01	0.69 (0.63, 0.74)
Fracture history (subgroup difference *p*=0.02*)	Intercept	0.78 (0.72, 0.84)	<0.001	
	Not fractured	*ref.*		0.78 (0.72, 0.84)
	Mixed	-0.13 (-0.22, -0.04)	0.01	0.65 (0.59, 0.72)
Age group (subgroup difference *p*=0.97*)	Intercept	0.72 (0.66, 0.79)	<0.001	
	<70	*ref.*		0.72 (0.66, 0.79)
	≥70	0.00(-0.10, 0.10)	0.97	0.72 (0.64, 0.81)

HSUV, Health state utility value, HUI, Health utility index, SG, Standard gamble, VAS, Visual analogue scale.

*Significance of subgroup was determined by Wald test.

** Mean difference from the reference value.

Table 3.5 Multivariable meta-regressions

Category	Pre-fracture		Post-hip fracture		Post-vertebral fracture		Post-wrist fracture	
	Variable	**Coef. *** (S.E.)**	**Variable**	**Coef. *** (S.E.)**	**Variable**	**Coef. *** (S.E.)**	**Variable**	**Coef. *** (S.E.)**
Time after fracture	Immediate	NA	Immediate	*ref.*	Immediate	*ref.*	Immediate	*ref.*
	First year	NA	First year	0.25 (0.04) *	First year	0.16 (0.04) *	First year	0.20 (0.04) *
	Subsequent years	NA	Subsequent years	0.27 (0.05) *	Subsequent years	0.21 (0.04) *	Subsequent years	0.25 (0.06) *
Age	<60	*ref.*	<70	*ref.*	<70	*ref.*	<70	*ref.*
	60-69	-0.05 (0.05) **	70-74	0.04 (0.05) **	70-74	-0.19 (0.04) *	≥70	-0.03 (0.06) **
	70-79	-0.12 (0.05) *	75-79	0.06 (0.05) **	≥75	-0.18 (0.04) *		
	≥80	-0.12 (0.05) *	≥80	-0.05 (0.06) **				
HSUV elicitation method	EQ-5D	*ref.*	EQ-5D	*ref.*	EQ-5D	*ref.*	EQ-5D	*ref.*
	VAS	-0.11 (0.02) *	VAS	0.04 (0.04) **	VAS	-0.02 (0.03) **	VAS	0.15 (0.11) **
	others	-0.01 (0.02) **	others	0.15 (0.06) *	others	0.22 (0.04) *	others	0.17 (0.09) **
HSUV type	Not retrospective	*ref.*	Not retrospective	NA	Not retrospective	NA	Not retrospective	NA
	Retrospective	0.06 (0.02) *	Retrospective	NA	Retrospective	NA	Retrospective	NA
Sex	Female	NA	Female	*ref.*	Female	*ref.*	Female	*ref.*
	Mixed	NA	Mixed	0.02 (0.12) **	Mixed	0.01 (0.07) **	Mixed	0.15 (0.33) **
Fracture history	Not fractured	NA	Not fractured	*ref.*	Not fractured	*ref.*	Not fractured	*ref.*
	Mixed	NA	Mixed	-0.18 (0.04) *	Mixed	-0.11 (0.03) *	Mixed	-0.02 (0.06) **
Constant		0.84 (0.05)		0.34 (0.07)		0.58 (0.08)		0.44 (0.29)
I^2		0.99		0.98		0.98		0.99
R^2		0.31		0.63		0.45		0.56

HSUV, Health state utility value, VAS, Visual analogue scale, S.E. standard error, NA, not applicable in multivariable meta-regression.

* p<0.05, ** not significant, ***coefficient: the mean difference from Constant statistic.

3.6 Discussion

To date, this is the largest meta-analysis evaluating health-related HSUVs for osteoporosis and osteoporotic fracture related conditions. Former reviews have provided more general HSUVs for osteoporotic fracture conditions, while we have determined the HSUV point and interval estimates, as well as HSUV prediction models for osteoporotic pre-fracture and post-fracture conditions, which allow cost effectiveness modellers in osteoporosis contexts to incorporate HSUV interval estimates in probabilistic sensitivity analyses [34]. This study confirmed that the HSUVs for fracture conditions were lower than that for the pre-fracture condition [16, 20]. Furthermore, our study expanded the previous work in four ways: first, by including more studies, meta-regressions were performed to identify both within study variance and between study heterogeneities. Second, the review provides data that were not available in previous reviews, such as HSUVs for subsequent years after vertebral fracture; third, specific contributors for HSUV heterogeneities such as patient's age, time after fracture and utility elicitation method were addressed through meta-regressions; and finally, HSUV prediction models were provided that incorporated significant covariates.

Previously it has been assumed that there is no HSUV loss for the "osteoporosis without fracture" condition versus the general population [16], and our estimates confirmed this when comparing the age-specific HSUVs (*Table 3.1*) with the UK normative dataset of HSUVs for the general population [35].

Our study has shown that hip fracture had the highest impact on HSUV. However, HSUV for post-hip fracture improved significantly with time thereafter (*Table 3.2*). HSUV for first year post-hip fracture was even higher than that of post-vertebral facture (0.59 versus 0.55), but still lower than post-wrist fracture (HSUV=0.78). Interestingly, HSUVs for subsequent years after hip and vertebral fractures were equivalent and lower than that of post-wrist fracture (0.66 versus 0.81).

A previous study suggested that retrospective HSUV would overestimate the HSUV due to recall bias [18]. Our findings supported this: the retrospectively reported HSUV was 0.05 higher than what was reported at the time of fracture.

Quality adjusted life years (QALYs) derived from HSUVs were widely used in health technology assessments on osteoporotic fracture preventions [5-7, 36]. Whilst different instruments provide varied HSUVs, EQ-5D is still preferred by NICE as the instrument for

calculating HSUVs for adult populations unless it was unavailable or proved inappropriate [37]. Standard gamble provided higher HSUVs compared with EQ-5D for all conditions. Similar evidence was found for other diseases such as chronic kidney disease [38] and breast cancer [39]. Our result suggested the HSUV elicited from the VAS was greater than that from the EQ-5D for the pre-fracture condition, but conversely lower for the post-hip fracture condition. This apparent contradiction has been discussed in a previous review [16] and has been supported by a number of subsequent studies [40]. Given the discrepancy of HSUVs from different elicitation methods evaluating the same health status, there is a need to adopt international standard methods, in particular the EQ-5D, to measure the utility-based quality of life for osteoporosis related conditions.

Conventionally, the male study population was expected to have higher HSUVs than the female population, with this difference explained by socio-demographic and socio-economic status [41]. However, our results suggested the female study population had higher HSUVs than mixed population: the mixed population had 0.11, 0.15 and 0.13 lower HSUV comparing with that of female population. However, the differences were not significant when accounting for other covariates. In our analysis we were unable to perform a comparison between female and male HSUV due to the paucity of data on HSUV for male populations.

A number of studies indicated an additional decrement in HSUVs for patients with prevalent/pre-existing fractures [10, 18], particularly in vertebral fracture patients [40]. Our findings, however, suggested that if a patient had a past history of fracture, there was a more dramatic impact of new hip fractures on HSUVs. The HSUV difference between patients with prevalent fracture and patients without prevalent fracture was -0.31 (95% CI: -0.39, -0.23): this difference was still significant after adjusting for time after fracture. This question may be addressed further clarified by future analysis of patient-level data from trials such as the International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS) [18].

The explanatory power of the pre-fracture HSUV prediction model was weak, with an R-squared value of 0.31. However, the post-fracture HSUV models performed fairly well, given an R-squared value of nearly 0.50 or greater. The reason for the weak prediction for pre-fracture could be explained by the complexity of the pre-fracture population, since the population characteristics were often unknown. Treatment history, fear of falling, bone profile and comorbidities were potential contributors to HSUVs [42]. Accounting for these parameters was not feasible in aggregated level data, therefore the explanatory power for pre-

fracture HSUV prediction was weak.

The strengths of this review were three-fold: first, this review included 362 HSUVs from 142,477 patients; substantially larger than in size than previous reviews [16, 20]. It completed the missing evidence from previous reviews [16, 20] due to the paucity of data. Second, this review performed meta-regression analyses that indicated HSUV disparity within the patients' demographic characteristics such as sex, age and history of fracture. And third, HSUVs prediction algorithms were provided for pre- and post-fracture conditions.

There were a number of limitations to this study. It was not feasible to specify the treatment that potentially affected patients' HSUVs. Surgical management of osteoporotic vertebral fractures resulted in a higher HSUV than non-surgical management [43].Severity of fractures could be a contributor to HSUVs, but it was not possible to ascertain the severity of fractures from aggregate data. HSUV for morphometric vertebral fracture was estimated differ from that of fractures with clinical diagnosis [16, 44]. Similarly, hip fracture patients ending in nursing home tended to have lower HSUV that of patients with independent mobility [44]. Accordingly, patients with worse prognoses were expected to have a lower HSUV comparing with patients with better prognoses. A number of studies reported HSUVs at multiple time points after fractures [17, 18] that tended to be stochastically dependent, as they came from the same population. However, the HSUVs were analysed independently in our study ignoring the correlation between time points [45]. Finally, meta-regressions performed in this study were univariate meta-regressions that explored particular covariates' contribution to between-study heterogeneity [33]. However, the I^2 statistic was greater than 0.75 in all analyses which indicates considerable heterogeneity remained [26] and a large part of the between study variation remained unexplained by the factors we examined. It is likely that other variables, such as co-morbidities, severity of the fracture, that potentially affect the HSUVs contribute to this heterogeneity, but we were not able to assess this due to the lack of availability of aggregated-level data. As the development of the methodology for synthesizing HSUVs from multiple studies is at an early stage, the validity of apply conventional meta-analytic techniques to HSUV data is not well understood [22]. Improvements in synthesizing HSUVs will be achieved with further progress in this area.

This study is the largest meta-analysis conducted on HSUV on osteoporotic fracture context with subgroup analyses performed for the first time through meta-regressions. Furthermore, this study provided prediction models that incorporate variables that contributed to HSUVs.

This study confirmed that fracture events had substantial impact on osteoporotic patients in terms of quality of life. Specifically, HSUVs after hip and vertebral fracture were dramatically decreased. Additional decrements of HSUVs were found in hip and vertebral fracture patients with prevalent fractures. These findings can be applied in future health economic evaluations investigating cost effectiveness of osteoporotic fracture preventions, and may also be useful for studies on cost effectiveness of post-fracture interventions aiming at improving the quality of life after fracture.

3.7 Postscript

Despite a large number of participants included in the meta-analysis, most of the included populations were Caucasian and therefore there is a small chance that the results might not be applicable to other populations. To address this concern, HSUV multipliers, which quantify the proportionate effect of a fracture on the baseline population HSUV were derived from this meta-analysis. For example, the HSUV multiplier for the first year after a hip fracture was set at 0.776 and this value was combined with the HSUV for the Chinese general population to calculate the HSUVs for the first year after a hip fracture. Using the HSUV multipliers enables the quantification of the effects of fractures on HSUVs and also accounts for Chinese-specific population HSUVs.

3.8 References

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45. Trikalinos TA, Olkin I (2012) Meta-analysis of effect sizes reported at multiple time points: A multivariate approach. Clinical Trials 9:610-620

Appendix 3B.1 Search strategy in MEDLINE

1. *Osteoporosis/
2. *Bone Disease, Metabolic/
3. osteoporo$.ti
4. or/1-3
5. (bone adj6 densit*).ti
6. *Bone Density/
7. (bone or bones).ti
8. *densitometry/
9. *Tomography, X-Ray Computed/
10. densit*.ti
11. 9 and 10
12. 8 or 11
13. 7 and 12
14. 5 or 6 or 13
15. *Colles' Fracture/
16. *hip fractures/
17. *Spinal Fractures/
18. *Fractures, Shoulder/
19. or/ 15-18
20. *Fractures, Bone/
21. fractur*.ti
22. or/19-21
23. colles*.ti
24. (hip or hips).ti
25. (femur adj6 neck).ti
26. (femural adj6 neck).ti
27. (spine or spinal).ti
28. vetebra*.ti
29. *Lumbar Vertebrae/
30. or/23-29
31. 22 and 30
32. *Estrogen Replacement Therapy/
33. (estrogen replacement therapy).ti
34. (oestrogen replacement therapy).ti
35. (hormone replacement therapy).ti
36. ert.ti
37. ort.ti
38. hrt.ti
39. or/32-38
40. *menopause/
41. *Climacteric/
42. menopaus*.ti
43. postmenopaus*.ti
44. climacteric.ti
45. or/40-44
46. 39 or 45
47. 31 and 46
48. 4 or 14 or 47
49. *Quality of life/
50. *QALY/
51. *Health status/
52. *Health status indicators/
53. or/49-52
54. (quality of life).tw
55. (life quality).tw
56. hql.tw
57. qol.tw
58. (euroqol or eq 5d or eq5d).tw
59. qaly*.tw
60. (quality adjusted life year*).tw
61. hye*.tw
62. (health* year* equivalent*).tw
63. (health utility*).tw
64. (hui or hui1 or hui2 or hui3).tw
65. (quality of wellbeing*).tw
66. (quality of well being).tw
67. qwb.tw
68. (qald* or qale* or qtime*).tw
69. (standard gambl*).tw
70. (time trade off).tw
71. (time tradeoff).tw
72. tto.tw
73. (visual analog* scale*).tw
74. (discrete choice experiment*).tw
75. (health state* utility*).tw
76. (health state* value*).tw
77. (health state* preference*).tw
78. or/54-77
79. 78 or 53
80. letter.pt
81. editorial.pt
82. comment.pt
83. or/80-82
84. 79 not 83
85. 48 and 84

Appendix 3B.2: A list of all included studies in the systematic review

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3. Hall SE, Criddle RA, Comito TL, Prince RL (1999) A case-control study of quality of life and functional impairment in women with long-standing vertebral osteoporotic fracture. Osteoporosis International 9:508-515
4. Oleksik A, Lips P, Dawson A, Minshall ME, Shen W, Cooper C, Kanis J (2000) Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research, pp 1384-1392
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8. Tosteson AN, Gabriel SE, Grove MR, Moncur MM, Kneeland TS, Melton LJ, 3rd (2001) Impact of hip and vertebral fractures on quality-adjusted life years. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 12:1042-1049
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fractures in the elderly: functional outcome and quality of life according to EuroQol. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 11:473-481

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29. Iglesias CP, Manca A, Torgerson DJ (2009) The health-related quality of life and cost implications of falls in elderly women. Osteoporosis International 20:869-878
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31. Van Schoor NM, Yu H, Bobula J, Lips P (2009) Cross-geographic region differences in quality of life in women with and without vertebral fracture. Osteoporosis International 20:1759-1766
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Appendix 3B.3: Characteristics of included studies in the systematic review

Category	Pre-fracture		Post-hip fracture		Post-vertebral fracture		Post-wrist fracture	
	Variable	Number of HSUVs (%)	Variable	Number of HSUVs (%)	Variable	Number of HSUVs (%)	Variable	Number of HSUVs (%)
Time after fracture	Immediate	NA	Immediate	14 (16%)	Immediate	22 (17%)	Immediate	13 (35%)
	First year	NA	First year	34 (38%)	First year	45 (35%)	First year	19 (51%)
	Subsequent years	NA	Subsequent years	41 (46%)	Subsequent years	63 (48%)	Subsequent years	5 (14%)
Age	<60	7 (7%)	<70	7 (8%)	<70	30 (23%)	<70	23 (62%)
	60-69	38 (36%)	70-74	25 (28%)	70-74	52 (40%)	≥70	14 (38%)
	70-79	46 (43%)	75-79	42 (47%)	≥75	48 (37%)		
	≥80	15 (14%)	≥80	15 (17%)				
HSUV elicitation method	EQ-5D	73 (72%)	EQ-5D	58 (65%)	EQ-5D	93 (71%)	EQ-5D	30 (81%)
	HUI	3 (3%)	HUI	3 (4%)	HUI	3 (2%)	HUI	2 (5%)
	Rating scale	2 (2%)	QWB	1 (1%)	QWB	2 (2%)	SG	2 (5%)
	SF-36	1 (1%)	SG	2 (2%)	SG	2 (2%)	Rating scale	1 (4%)
	SG	2 (2%)	TTO	3 (4%)	TTO	6 (5%)	VAS	2 (5%)
	TTO	5 (5%)	Rating scale	2 (2%)	Rating scale	2 (2%)		
	VAS	17 (16%)	VAS	20 (22%)	VAS	22 (16%)		
HSUV type	Not retrospective	60 (43%)	Not retrospective	NA	Not retrospective	NA	Not retrospective	NA
	Retrospective	46 (57%)	Retrospective	NA	Retrospective	NA	Retrospective	NA
Sex	Female	52 (49%)	Female	17 (19%)	Female	39 (30%)	Female	11 (30%)
	Mixed	54 (51%)	Mixed	72 (81%)	Mixed	91 (70%)	Mixed	26 (70%)
Fracture history	Not fractured	62 (59%)	Not fractured	69 (78%)	Not fractured	72 (55%)	Not fractured	20 (54%)
	Mixed	44 (41%)	Mixed	20 (22%)	Mixed	58 (45%)	Mixed	17 (46%)
Country	Asian	10 (9%)	Asian	4 (5%)	Asian	9 (7%)	Asian	0 (0%)
	Not Asian	96 (91%)	Not Asian	85 (95%)	Not Asian	121 (93%)	Not Asian	100 (100%)
Total		106 (100%)		89 (100%)		130 (100%)		37 (100%)

HSUV, Health state utility value, HUI, Health utility index, QWB, Quality of well-being, SG, Standard gamble, TTO, Time trade-off, VAS, Visual analogue scale

Appendix 3B.4 Table 1: Characteristics of reviewed studies for pre-fractures

Studies	Countries	Sample size	HSUV elicitation method	Mean age	Female(%)	Retrospective	HSUV	Standard deviation of HSUV
Gabriel 1999	US	75	TTO	76.0	100%	Y	0.840	0.290
Gabriel 1999	US	199	TTO	68.0	100%	N	0.430	0.400
Hall 1999	Australia	100	SF-36	74.3	100%	N	0.720	0.070
Oleksik 2000	Europe	302	EQ-5D	66.2	100%	N	0.822	0.021
Salkeld 2000	Australia	203	EQ-5D	83.0	100%	N	0.770	NA
Salkeld 2000	Australia	120	TTO	80.0	100%	N	0.700	NA
Salkeld 2000	Australia	120	TTO	>=85	100%	N	0.620	NA
Cranney 2001	Canada	11	Rating scale	56.0	100%	N	0.920	0.080
Cranney 2001	Canada	11	SG	56.0	100%	N	0.900	0.110
Cranney 2001	Canada	11	HUI	56.0	100%	N	0.800	0.100
Cranney 2001	Canada	11	Rating scale	56.0	100%	N	0.880	0.120
Cranney 2001	Canada	11	SG	56.0	100%	N	0.930	0.070
Cranney 2001	Canada	11	HUI	56.0	100%	N	0.820	0.070
Tosteson 2001	US	199	TTO	67.4	100%	N	0.910	0.216
Tidermark 2002	Sweden	89	EQ-5D	79.9	76%	Y	0.780	0.210
Cockerill 2004	Europe	136	EQ-5D	64.1	77%	N	0.825	0.160
Cockerill 2004	Europe	136	VAS	64.1	77%	N	0.699	0.215
Blomfeldt 2005	Sweden	49	EQ-5D	79.2	82%	Y	0.800	0.220
Blomfeldt 2005	Sweden	53	EQ-5D	81.4	79%	Y	0.840	0.130
Dhillon 2005	UK	159	EQ-5D	65.0	96%	N	0.650	0.280
Dhillon 2005	UK	159	VAS	65.0	96%	N	0.680	0.200
Sawka 2005	Canada	421	HUI	>65	73%	N	0.690	0.270
van Schoor 2005	the Netherlands	152	EQ-5D	>65	52%	N	0.800	NA
Yoh 2005	Japan	19	EQ-5D	>60	100%	N	0.750	0.150

Appendix 3B.4 Table 1: Characteristics of reviewed studies for pre-fracture

Studies	Countries	Sample size	HSUV elicitation method	Mean age	Female(%)	Retrospective	HSUV	Standard deviation of HSUV
Borgstrom 2006	Sweden	277	EQ-5D	77.6	78%	Y	0.800	0.015
Borgstrom 2006	Sweden	81	EQ-5D	75.0	81%	Y	0.730	0.031
Borgstrom 2006	Sweden	276	EQ-5D	69.5	91%	Y	0.890	0.010
Soderqvist 2006	Sweden	163	EQ-5D	82.8	82%	Y	0.640	0.290
Salaffi 2007	Italy	244	EQ-5D	68.1	100%	N	0.710	0.157
Salaffi 2007	Italy	244	VAS	68.1	100%	N	0.605	0.190
Cooper 2008	Europe	830	EQ-5D	70.6	100%	N	0.530	0.320
Cooper 2008	Europe	830	EQ-5D	70.6	100%	N	0.590	0.280
Cooper 2008	Europe	830	EQ-5D	70.6	100%	N	0.620	0.280
Cooper 2008	Europe	843	VAS	70.6	100%	N	0.559	0.188
Cooper 2008	Europe	843	VAS	70.6	100%	N	0.581	0.183
Cooper 2008	Europe	843	VAS	70.6	100%	N	0.609	0.188
Sugeno 2008	Japan	50	EQ-5D	77.4	80%	Y	0.772	0.235
Sugeno 2008	Japan	50	VAS	77.4	80%	Y	0.626	0.217
van Schoor 2008	Europe	271	EQ-5D	66.2	100%	N	0.820	0.010
van Schoor 2008	Europe	120	EQ-5D	64.4	79%	N	0.820	0.015
Ekstrom 2009	Sweden	87	EQ-5D	82.5	75%	Y	0.730	NA
van Schoor 2009	Africa	55	EQ-5D	66.8	100%	N	0.850	NA
van Schoor 2009	Asia	37	EQ-5D	65.6	100%	N	0.760	NA
van Schoor 2009	Europe	1034	EQ-5D	65.5	100%	N	0.770	NA
van Schoor 2009	Oceania	38	EQ-5D	66.3	100%	N	0.900	NA
van Schoor 2009	S. America	1477	EQ-5D	65.9	100%	N	0.840	NA
van Schoor 2009	N. America	447	EQ-5D	65.1	100%	N	0.820	NA
Rajzbaum 2009	France	409	EQ-5D	67.0	100%	N	0.770	0.200
Rajzbaum 2009	France	409	VAS	67.0	100%	N	0.723	0.143
Adachi 2010	International	42577	EQ-5D	68.7	100%	N	0.790	0.200

Appendix 3B.4 Table 1: Characteristics of reviewed studies for pre-fracture

Studies	Countries	Sample size	HSUV elicitation method	Mean age	Female(%)	Retrospective	HSUV	Standard deviation of HSUV
Bianchi 2010	Italy	59	EQ-5D	81.0	100%	Y	0.880	0.020
Bianchi 2010	Italy	59	VAS	81.0	100%	Y	0.800	0.015
Dennison 2010	UK	2567	EQ-5D	68.4	100%	N	0.760	0.230
Dennison 2010	UK	1512	EQ-5D	70.7	100%	N	0.830	0.200
Dimai 2010	Austria	95	EQ-5D	71.0	80.0%	Y	0.800	0.026
Dimai 2010	Austria	66	EQ-5D	71.0	80.0%	Y	0.870	0.036
Lekander 2010	Russia	184	EQ-5D	65.0	81.0%	Y	0.730	0.015
Lekander 2010	Russia	216	EQ-5D	65.0	81.0%	Y	0.900	0.010
Muraki 2010	Japan	678	EQ-5D	69.7	0.0%	N	0.910	0.140
Thomas 2010	France	42	EQ-5D	72.0	82.0%	Y	0.650	0.046
Thomas 2010	France	85	EQ-5D	72.0	82.0%	Y	0.800	0.026
Togawa 2010	Japn	30	EQ-5D	78.0	87.5%	Y	0.907	NA
Togawa 2010	Japn	10	EQ-5D	78.0	87.5%	Y	0.736	NA
Adami 2011	Italy	34	EQ-5D	72.9	90.5%	N	0.610	0.290
Adami 2011	Italy	37	VAS	72.9	90.5%	N	0.545	0.230
Aloumanis 2011	Greece	301	VAS	69.5	100%	N	0.540	0.250
Aloumanis 2011	Greece	275	VAS	69.5	100%	N	0.800	0.190
Chico 2012	Mexico	452	EQ-5D	71.8	86%	Y	0.680	0.310
Chico 2012	Mexico	452	VAS	71.8	86%	Y	0.794	0.185
Nakamura 2012	Japan	1069	EQ-5D	73.5	100%	N	0.706	0.199
Nakamura 2012	Japan	1069	VAS	73.5	100%	N	0.637	0.193
Nakamura 2012	Japan	1069	EQ-5D	73.5	100%	N	0.780	0.189
Nakamura 2012	Japan	1069	EQ-5D	73.5	100%	N	0.804	0.192
Tadic 2012	Serbia	50	EQ-5D	63.0	100%	N	0.580	0.200
Tadic 2012	Serbia	50	VAS	63.0	100%	N	0.505	0.232
Voigt 2012	Germany	95	VAS	60.9	0%	N	0.745	0.178

Appendix 3B.4 Table 1: Characteristics of reviewed studies for pre-fracture

Studies	Countries	Sample size	HSUV elicitation method	Mean age	Female(%)	Retrospective	HSUV	Standard deviation of HSUV
Yoh 2012	Japan	491	EQ-5D	70.7	100%	N	0.700	0.170
Yoh 2012	Japan	389	EQ-5D	70.7	100%	N	0.760	0.160
Yoh 2012	Japan	303	EQ-5D	70.7	100%	N	0.770	0.170
Borgstrom 2013	Austria	266	EQ-5D	76.2	76%	Y	0.750	0.015
Borgstrom 2013	Spain	46	EQ-5D	80.4	78%	Y	0.660	0.056
Borgstrom 2013	France	197	EQ-5D	76.7	78%	Y	0.790	0.015
Borgstrom 2013	Italy	112	EQ-5D	79.4	96%	Y	0.850	0.020
Borgstrom 2013	Lithuania	34	EQ-5D	74.9	79%	Y	0.800	0.026
Borgstrom 2013	Mexico	44	EQ-5D	78.8	82%	Y	0.640	0.046
Borgstrom 2013	Russia	219	EQ-5D	68.9	70%	Y	0.710	0.015
Borgstrom 2013	Sweden	355	EQ-5D	77.5	79%	Y	0.800	0.015
Borgstrom 2013	Austria	113	EQ-5D	67.9	92%	Y	0.860	0.015
Borgstrom 2013	Australia	50	EQ-5D	68.1	86%	Y	0.910	0.026
Borgstrom 2013	France	168	EQ-5D	68.4	90%	Y	0.830	0.015
Borgstrom 2013	Italy	30	EQ-5D	75.0	96%	Y	0.940	0.020
Borgstrom 2013	Russia	202	EQ-5D	62.6	86%	Y	0.880	0.010
Borgstrom 2013	Sweden	390	EQ-5D	69.2	92%	Y	0.900	0.010
Borgstrom 2013	USA	34	EQ-5D	69.3	82%	Y	0.870	0.031
Borgstrom 2013	Austria	71	EQ-5D	72.5	79%	Y	0.780	0.036
Borgstrom 2013	France	76	EQ-5D	72.1	72%	Y	0.660	0.041
Borgstrom 2013	Italy	47	EQ-5D	72.7	98%	Y	0.930	0.026
Borgstrom 2013	Russia	197	EQ-5D	67.8	89%	Y	0.790	0.015
Borgstrom 2013	Sweden	120	EQ-5D	76.5	80%	Y	0.740	0.020
Borgstrom 2013	USA	37	EQ-5D	75.8	73%	Y	0.750	0.041
Buecking 2013	Germany	350	EQ-5D	81.0	27%	Y	0.710	0.290
Buecking 2013	Germany	350	VAS	81.0	27%	Y	0.570	0.230

Appendix 3B.4 Table 1: Characteristics of reviewed studies for pre-fracture

Studies	Countries	Sample size	HSUV elicitation method	Mean age	Female(%)	Retrospective	HSUV	Standard deviation of HSUV
Guillemin 2013	International	1143	EQ-5D	45-54	100%	N	0.810	0.230
Guillemin 2013	International	2638	EQ-5D	55-64	100%	N	0.780	0.250
Guillemin 2013	International	2366	EQ-5D	65-74	40.0%	N	0.740	0.260
Guillemin 2013	International	1686	EQ-5D	>=75	40.0%	N	0.670	0.290

HSUV, Health state utility value, HUI, Health utility index, SG, Standard gamble, TTO, Time trade-off, VAS, Visual analogue scale

Appendix 3B.4 Table 2: Characteristics of reviewed studies for post-hip fracture

Studies	Countries	Sample size	HSUV elicitation method	Mean age	Female (%)	Recurrent fractures (%)	Time after fracture (months)	HSUV	Standard deviation of HSUV
Cranney 2001	Canada	10	rating scale	79.5	100%	0%	0	0.710	0.110
Cranney 2001	Canada	10	SG	79.5	100%	0%	0	0.910	0.120
Cranney 2001	Canada	10	HUI	79.5	100%	0%	0	0.670	0.120
Borgstrom 2006	Sweden	277	EQ-5D	77.6	78%	23%	0	0.180	0.015
Sugeno 2008	Japan	50	EQ-5D	77.4	80%	0%	0	0.669	0.205
Sugeno 2008	Japan	50	VAS	77.4	80%	0%	0	0.641	0.220
Borgstrom 2013	Austria	266	EQ-5D	76.20	76%	19%	0	0.190	0.250
Borgstrom 2013	Spain	46	EQ-5D	80.40	78%	33%	0	0.030	0.104
Borgstrom 2013	France	197	EQ-5D	76.70	78%	19%	0	0.090	0.215
Borgstrom 2013	Italy	112	EQ-5D	79.40	96%	15%	0	0.040	0.162
Borgstrom 2013	Lithuania	34	EQ-5D	74.90	79%	9%	0	0.010	0.030
Borgstrom 2013	Mexico	44	EQ-5D	78.80	82%	9%	0	0.010	0.068
Borgstrom 2013	Russia	219	EQ-5D	68.90	70%	25%	0	0.030	0.151
Borgstrom 2013	Sweden	355	EQ-5D	77.50	79%	22%	0	0.180	0.192
Gabriel 1999	US	37	HUI	76	100%	0%	36	0.680	0.180
Gabriel 1999	US	37	QWB	76	100%	0%	36	0.610	0.080
Gabriel 1999	US	37	VAS	76	100%	0%	36	0.720	0.160
Gabriel 1999	US	37	TTO	76	100%	0%	36	0.700	0.410
Cranney 2001	Canada	10	rating scale	79.5	100%	0%	2	0.760	0.180
Cranney 2001	Canada	10	SG	79.5	100%	0%	2	0.840	0.180
Cranney 2001	Canada	10	HUI	79.5	100%	0%	2	0.710	0.090
Tosteson 2001	US	35	TTO	80.3	100%	0%	18	0.480	0.483
Tosteson 2001	US	32	TTO	80.3	100%	0%	24	0.790	0.375
Tidermark 2002	Sweden	71	EQ-5D	79.90	76%	0%	0.25	0.440	0.330

Appendix 3B.4 Table 2: Characteristics of reviewed studies for post-hip fracture

Studies	Countries	Sample size	HSUV elicitation method	Mean age	Female (%)	Recurrent fractures (%)	Time after fracture (months)	HSUV	Standard deviation of HSUV
Tidermark 2002	Sweden	79	EQ-5D	79.90	76%	0%	4	0.550	0.370
Tidermark 2002	Sweden	69	EQ-5D	79.90	76%	0%	17	0.510	0.360
Zethraeus 2002	Sweden	86	EQ-5D	75	62%	0%	0.5	0.420	0.320
Zethraeus 2002	Sweden	65	EQ-5D	75	62%	0%	6	0.640	0.270
Zethraeus 2002	Sweden	58	EQ-5D	75	62%	0%	9	0.600	0.310
Zethraeus 2002	Sweden	46	EQ-5D	75	62%	0%	12	0.580	0.310
Zethraeus 2002	Sweden	82	VAS	75	62%	0%	0.5	0.540	0.200
Zethraeus 2002	Sweden	66	VAS	75	62%	0%	6	0.640	0.210
Zethraeus 2002	Sweden	55	VAS	75	62%	0%	9	0.620	0.230
Zethraeus 2002	Sweden	44	VAS	75	62%	0%	12	0.640	0.230
Tidermark 2003	Sweden	10	EQ-5D	73.4	30%	0%	38	0.620	0.264
Blomfeldt 2005	Sweden	49	EQ-5D	79.20	82%	0%	4	0.730	NA
Blomfeldt 2005	Sweden	53	EQ-5D	81.40	79%	0%	4	0.600	NA
Blomfeldt 2005	Sweden	49	EQ-5D	79.20	82%	0%	12	0.730	NA
Blomfeldt 2005	Sweden	53	EQ-5D	81.40	79%	0%	12	0.630	NA
Blomfeldt 2005	Sweden	49	EQ-5D	79.20	82%	0%	24	0.700	NA
Blomfeldt 2005	Sweden	53	EQ-5D	81.40	79%	0%	24	0.640	NA
Blomfeldt 2005	Sweden	34	EQ-5D	79.20	82%	0%	48	0.620	0.310
Blomfeldt 2005	Sweden	21	EQ-5D	81.40	79%	0%	48	0.520	0.400
Borgstrom 2006	Sweden	277	EQ-5D	77.6	78%	23%	4	0.620	0.015
Borgstrom 2006	Sweden	277	EQ-5D	77.6	78%	23%	12	0.670	0.015
Jakob 2006	Europe	1309	EQ-5D	71.2	100%	0%	14.5	0.470	0.340
Jakob 2006	Europe	1309	VAS	71.2	100%	0%	14.5	0.521	0.192
Jakob 2006	Europe	1005	EQ-5D	69	100%	0%	15.8	0.530	0.320
Jakob 2006	Europe	1005	VAS	69	100%	0%	15.8	0.563	0.191
Soderqvist 2006	Sweden	163	EQ-5D	82.80	82%	0%	4	0.430	NA

Appendix 3B.4 Table 2: Characteristics of reviewed studies for post-hip fracture

Studies	Countries	Sample size	HSUV elicitation method	Mean age	Female (%)	Recurrent fractures (%)	Time after fracture (months)	HSUV	Standard deviation of HSUV
Soderqvist 2006	Sweden	163	EQ-5D	82.80	82%	0%	12	0.490	NA
Sugeno 2008	Japan	50	EQ-5D	77.4	80%	0%	12	0.807	0.166
Sugeno 2008	Japan	50	VAS	77.4	80%	0%	12	0.796	0.168
Ekstrom 2009	Sweden	87	EQ-5D	82.50	75%	0%	4	0.530	NA
Ekstrom 2009	Sweden	87	EQ-5D	82.50	75%	0%	12	0.530	NA
Ekstrom 2009	Sweden	87	EQ-5D	82.50	75%	0%	24	0.520	NA
Adachi 2010	International	1074	EQ-5D	68.66	100%	0%	18	0.640	0.300
Lekander 2010	Russia	184	EQ-5D	65.00	81%	25%	12	0.510	0.026
Adachi 2011	International	1005	EQ-5D	74.41	76.7%	0.0%	3	0.580	0.317
Adachi 2011	International	1005	EQ-5D	74.59	75.5%	0.0%	3	0.570	0.317
Adachi 2011	International	996	VAS	74.41	76.7%	0.0%	3	0.658	0.177
Adachi 2011	International	1002	VAS	74.59	75.5%	0.0%	3	0.657	0.184
Adachi 2011	International	808	VAS	74.41	76.7%	0.0%	6	0.715	0.151
Adachi 2011	International	775	VAS	74.59	75.5%	0.0%	6	0.718	0.150
Adachi 2011	International	738	VAS	74.41	76.7%	0.0%	12	0.740	0.158
Adachi 2011	International	711	VAS	74.59	75.5%	0.0%	12	0.733	0.157
Adachi 2011	International	450	VAS	74.41	76.7%	0.0%	24	0.748	0.168
Adachi 2011	International	413	VAS	74.59	75.5%	0.0%	24	0.725	0.169
Adachi 2011	International	101	VAS	74.41	76.7%	0.0%	36	0.716	0.204
Adachi 2011	International	83	VAS	74.59	75.5%	0.0%	36	0.707	0.189
Adachi 2011	International	814	EQ-5D	74.41	76.7%	0.0%	6	0.700	0.285
Adachi 2011	International	781	EQ-5D	74.59	75.5%	0.0%	6	0.690	0.279
Adachi 2011	International	742	EQ-5D	74.41	76.7%	0.0%	12	0.740	0.272
Adachi 2011	International	715	EQ-5D	74.59	75.5%	0.0%	12	0.710	0.267
Adachi 2011	International	457	EQ-5D	74.41	76.7%	0.0%	24	0.730	0.214
Adachi 2011	International	427	EQ-5D	74.59	75.5%	0.0%	24	0.720	0.207

Appendix 3B.4 Table 2: Characteristics of reviewed studies for post-hip fracture

Studies	Countries	Sample size	HSUV elicitation method	Mean age	Female (%)	Recurrent fractures (%)	Time after fracture (months)	HSUV	Standard deviation of HSUV
Adachi 2011	International	100	EQ-5D	74.41	76.7%	0.0%	36	0.660	0.300
Adachi 2011	International	83	EQ-5D	74.59	75.5%	0.0%	36	0.690	0.273
McDonough 2012	US	42	EQ-5D	68.1	72%	0%	36	0.780	0.150
Borgstrom 2013	Austria	266	EQ-5D	76.20	76%	19%	4	0.650	0.333
Borgstrom 2013	Spain	46	EQ-5D	80.40	78%	33%	4	0.640	0.208
Borgstrom 2013	France	197	EQ-5D	76.70	78%	19%	4	0.570	0.286
Borgstrom 2013	Italy	112	EQ-5D	79.40	96%	15%	4	0.450	0.270
Borgstrom 2013	Lithuania	34	EQ-5D	74.90	79%	9%	4	0.360	0.268
Borgstrom 2013	Mexico	44	EQ-5D	78.80	82%	9%	4	0.460	0.305
Borgstrom 2013	Russia	219	EQ-5D	68.90	70%	25%	4	0.430	0.378
Borgstrom 2013	Sweden	355	EQ-5D	77.50	79%	22%	4	0.620	0.288
Buecking 2013	Germany	277	EQ-5D	81	27%	0%	0.5	0.460	0.330
Buecking 2013	Germany	277	VAS	81	27%	0%	0.5	0.530	0.200

HSUV, Health state utility value, HUI, Health utility index, QWB, Quality of well-being, SG, Standard gamble, TTO, Time trade-off, VAS, Visual analogue scale

Appendix 3B.4 Table 3: Characteristics of reviewed studies for post-vertebral fracture

Studies	Countries	Sample size	HSUV elicitation method	Mean age	Female (%)	Recurrent fractures (%)	Time after fracture (months)	HSUV	Standard deviation of HSUV
Cranney 2001	Canada	10	rating scale	79.5	100%	0%	0	0.710	0.110
Cranney 2001	Canada	10	SG	79.5	100%	0%	0	0.910	0.120
Cranney 2001	Canada	10	HUI	79.5	100%	0%	0	0.670	0.120
Borgstrom 2006	Sweden	277	EQ-5D	77.6	78%	23%	0	0.180	0.015
Sugeno 2008	Japan	50	EQ-5D	77.4	80%	0%	0	0.669	0.205
Sugeno 2008	Japan	50	VAS	77.4	80%	0%	0	0.641	0.220
Borgstrom 2013	Austria	266	EQ-5D	76.20	76%	19%	0	0.190	0.250
Borgstrom 2013	Spain	46	EQ-5D	80.40	78%	33%	0	0.030	0.104
Borgstrom 2013	France	197	EQ-5D	76.70	78%	19%	0	0.090	0.215
Borgstrom 2013	Italy	112	EQ-5D	79.40	96%	15%	0	0.040	0.162
Borgstrom 2013	Lithuania	34	EQ-5D	74.90	79%	9%	0	0.010	0.030
Borgstrom 2013	Mexico	44	EQ-5D	78.80	82%	9%	0	0.010	0.068
Borgstrom 2013	Russia	219	EQ-5D	68.90	70%	25%	0	0.030	0.151
Borgstrom 2013	Sweden	355	EQ-5D	77.50	79%	22%	0	0.180	0.192
Gabriel 1999	US	37	HUI	76	100%	0%	36	0.680	0.180
Gabriel 1999	US	37	QWB	76	100%	0%	36	0.610	0.080
Gabriel 1999	US	37	VAS	76	100%	0%	36	0.720	0.160
Gabriel 1999	US	37	TTO	76	100%	0%	36	0.700	0.410
Cranney 2001	Canada	10	rating scale	79.5	100%	0%	2	0.760	0.180
Cranney 2001	Canada	10	SG	79.5	100%	0%	2	0.840	0.180
Cranney 2001	Canada	10	HUI	79.5	100%	0%	2	0.710	0.090
Tosteson 2001	US	35	TTO	80.3	100%	0%	18	0.480	0.483
Tosteson 2001	US	32	TTO	80.3	100%	0%	24	0.790	0.375
Tidermark 2002	Sweden	71	EQ-5D	79.90	76%	0%	0.25	0.440	0.330

Appendix 3B.4 Table 3: Characteristics of reviewed studies for post-vertebral fracture

Studies	Countries	Sample size	HSUV elicitation method	Mean age	Female (%)	Recurrent fractures (%)	Time after fracture (months)	HSUV	Standard deviation of HSUV
Tidermark 2002	Sweden	79	EQ-5D	79.90	76%	0%	4	0.550	0.370
Tidermark 2002	Sweden	69	EQ-5D	79.90	76%	0%	17	0.510	0.360
Zethraeus 2002	Sweden	86	EQ-5D	75	62%	0%	0.5	0.420	0.320
Zethraeus 2002	Sweden	65	EQ-5D	75	62%	0%	6	0.640	0.270
Zethraeus 2002	Sweden	58	EQ-5D	75	62%	0%	9	0.600	0.310
Zethraeus 2002	Sweden	46	EQ-5D	75	62%	0%	12	0.580	0.310
Zethraeus 2002	Sweden	82	VAS	75	62%	0%	0.5	0.540	0.200
Zethraeus 2002	Sweden	66	VAS	75	62%	0%	6	0.640	0.210
Zethraeus 2002	Sweden	55	VAS	75	62%	0%	9	0.620	0.230
Zethraeus 2002	Sweden	44	VAS	75	62%	0%	12	0.640	0.230
Tidermark 2003	Sweden	10	EQ-5D	73.4	30%	0%	38	0.620	0.264
Blomfeldt 2005	Sweden	49	EQ-5D	79.20	82%	0%	4	0.730	NA
Blomfeldt 2005	Sweden	53	EQ-5D	81.40	79%	0%	4	0.600	NA
Blomfeldt 2005	Sweden	49	EQ-5D	79.20	82%	0%	12	0.730	NA
Blomfeldt 2005	Sweden	53	EQ-5D	81.40	79%	0%	12	0.630	NA
Blomfeldt 2005	Sweden	49	EQ-5D	79.20	82%	0%	24	0.700	NA
Blomfeldt 2005	Sweden	53	EQ-5D	81.40	79%	0%	24	0.640	NA
Blomfeldt 2005	Sweden	34	EQ-5D	79.20	82%	0%	48	0.620	0.310
Blomfeldt 2005	Sweden	21	EQ-5D	81.40	79%	0%	48	0.520	0.400
Borgstrom 2006	Sweden	277	EQ-5D	77.6	78%	23%	4	0.620	0.015
Borgstrom 2006	Sweden	277	EQ-5D	77.6	78%	23%	12	0.670	0.015
Jakob 2006	Europe	1309	EQ-5D	71.2	100%	0%	14.5	0.470	0.340
Jakob 2006	Europe	1309	VAS	71.2	100%	0%	14.5	0.521	0.192
Jakob 2006	Europe	1005	EQ-5D	69	100%	0%	15.8	0.530	0.320
Jakob 2006	Europe	1005	VAS	69	100%	0%	15.8	0.563	0.191
Soderqvist 2006	Sweden	163	EQ-5D	82.80	82%	0%	4	0.430	NA

Appendix 3B.4 Table 3: Characteristics of reviewed studies for post-vertebral fracture

Studies	Countries	Sample size	HSUV elicitation method	Mean age	Female (%)	Recurrent fractures (%)	Time after fracture (months)	HSUV	Standard deviation of HSUV
Soderqvist 2006	Sweden	163	EQ-5D	82.80	82%	0%	12	0.490	NA
Sugeno 2008	Japan	50	EQ-5D	77.4	80%	0%	12	0.807	0.166
Sugeno 2008	Japan	50	VAS	77.4	80%	0%	12	0.796	0.168
Ekstrom 2009	Sweden	87	EQ-5D	82.50	75%	0%	4	0.530	NA
Ekstrom 2009	Sweden	87	EQ-5D	82.50	75%	0%	12	0.530	NA
Ekstrom 2009	Sweden	87	EQ-5D	82.50	75%	0%	24	0.520	NA
Adachi 2010	International	1074	EQ-5D	68.66	100%	0%	18	0.640	0.300
Lekander 2010	Russia	184	EQ-5D	65.00	81%	25%	12	0.510	0.026
Adachi 2011	International	1005	EQ-5D	74.41	76.7%	0.0%	3	0.580	0.317
Adachi 2011	International	1005	EQ-5D	74.59	75.5%	0.0%	3	0.570	0.317
Adachi 2011	International	996	VAS	74.41	76.7%	0.0%	3	0.658	0.177
Adachi 2011	International	1002	VAS	74.59	75.5%	0.0%	3	0.657	0.184
Adachi 2011	International	808	VAS	74.41	76.7%	0.0%	6	0.715	0.151
Adachi 2011	International	775	VAS	74.59	75.5%	0.0%	6	0.718	0.150
Adachi 2011	International	738	VAS	74.41	76.7%	0.0%	12	0.740	0.158
Adachi 2011	International	711	VAS	74.59	75.5%	0.0%	12	0.733	0.157
Adachi 2011	International	450	VAS	74.41	76.7%	0.0%	24	0.748	0.168
Adachi 2011	International	413	VAS	74.59	75.5%	0.0%	24	0.725	0.169
Adachi 2011	International	101	VAS	74.41	76.7%	0.0%	36	0.716	0.204
Adachi 2011	International	83	VAS	74.59	75.5%	0.0%	36	0.707	0.189
Adachi 2011	International	814	EQ-5D	74.41	76.7%	0.0%	6	0.700	0.285
Adachi 2011	International	781	EQ-5D	74.59	75.5%	0.0%	6	0.690	0.279
Adachi 2011	International	742	EQ-5D	74.41	76.7%	0.0%	12	0.740	0.272
Adachi 2011	International	715	EQ-5D	74.59	75.5%	0.0%	12	0.710	0.267
Adachi 2011	International	457	EQ-5D	74.41	76.7%	0.0%	24	0.730	0.214
Adachi 2011	International	427	EQ-5D	74.59	75.5%	0.0%	24	0.720	0.207

Appendix 3B.4 Table 3: Characteristics of reviewed studies for post-vertebral fracture

Studies	Countries	Sample size	HSUV elicitation method	Mean age	Female (%)	Recurrent fractures (%)	Time after fracture (months)	HSUV	Standard deviation of HSUV
Adachi 2011	International	100	EQ-5D	74.41	76.7%	0.0%	36	0.660	0.300
Adachi 2011	International	83	EQ-5D	74.59	75.5%	0.0%	36	0.690	0.273
McDonough 2012	US	42	EQ-5D	68.1	72%	0%	36	0.780	0.150
Borgstrom 2013	Austria	266	EQ-5D	76.20	76%	19%	4	0.650	0.333
Borgstrom 2013	Spain	46	EQ-5D	80.40	78%	33%	4	0.640	0.208
Borgstrom 2013	France	197	EQ-5D	76.70	78%	19%	4	0.570	0.286
Borgstrom 2013	Italy	112	EQ-5D	79.40	96%	15%	4	0.450	0.270
Borgstrom 2013	Lithuania	34	EQ-5D	74.90	79%	9%	4	0.360	0.268
Borgstrom 2013	Mexico	44	EQ-5D	78.80	82%	9%	4	0.460	0.305
Borgstrom 2013	Russia	219	EQ-5D	68.90	70%	25%	4	0.430	0.378
Borgstrom 2013	Sweden	355	EQ-5D	77.50	79%	22%	4	0.620	0.288
Buecking 2013	Germany	277	EQ-5D	81	27%	0%	0.5	0.460	0.330
Buecking 2013	Germany	277	VAS	81	27%	0%	0.5	0.530	0.200

HSUV, Health state utility value, HUI, Health utility index, QWB, Quality of well-being, SG, Standard gamble, TTO, Time trade-off, VAS, Visual analogue scale

Appendix 3B.4 Table 4: Characteristics of reviewed studies for post-wrist fracture

Studies	Countries	Sample size	HSUV elicitation method	Mean age	Female (%)	Recurrent fractures (%)	Time after fracture (months)	HSUV	Standard deviation of HSUV
Dolan 1999	UK	50	EQ-5D	71.5	100%	0%	0	0.539	0.162
Dolan 1999	UK	50	VAS	71.5	100%	0%	0	0.716	0.091
Cranney 2001	Canada	11	rating scale	68.0	100%	0%	0	0.840	0.110
Cranney 2001	Canada	11	SG	68.0	100%	0%	0	0.870	0.190
Cranney 2001	Canada	11	HUI	68.0	100%	0%	0	0.860	0.060
Borgstrom 2006	Sweden	276	EQ-5D	69.5	91%	14%	0	0.560	0.015
Borgstrom 2013	Austria	113	EQ-5D	67.9	92%	18%	0	0.490	0.011
Borgstrom 2013	Australia	50	EQ-5D	68.1	86%	12%	0	0.610	0.011
Borgstrom 2013	France	168	EQ-5D	68.4	90%	16%	0	0.370	0.008
Borgstrom 2013	Italy	30	EQ-5D	75.0	96%	7%	0	0.460	0.015
Borgstrom 2013	Russia	202	EQ-5D	62.6	86%	40%	0	0.450	0.013
Borgstrom 2013	Sweden	390	EQ-5D	69.2	92%	13%	0	0.560	0.006
Borgstrom 2013	USA	34	EQ-5D	69.3	82%	44%	0	0.640	0.034
Dolan 1999	UK	50	EQ-5D	71.5	100%	0%	1.6	0.925	0.097
Dolan 1999	UK	50	EQ-5D	71.5	100%	0%	1.6	0.908	0.063
Cranney 2001	Canada	11	rating scale	68.0	100%	0%	2	0.840	0.110
Cranney 2001	Canada	11	SG	68.0	100%	0%	2	0.870	0.190
Cranney 2001	Canada	11	HUI	68.0	100%	0%	2	0.860	0.060
Zethraeus 2002	Sweden	126	EQ-5D	72.0	88%	0%	0.5	0.540	0.270
Zethraeus 2002	Sweden	103	EQ-5D	72.0	88%	0%	6	0.760	0.220
Zethraeus 2002	Sweden	92	EQ-5D	72.0	88%	0%	9	0.810	0.210
Zethraeus 2002	Sweden	80	EQ-5D	72.0	88%	0%	12	0.820	0.200
Zethraeus 2002	Sweden	132	EQ-5D	72.0	88%	0%	0.5	0.640	0.220
Zethraeus 2002	Sweden	114	EQ-5D	72.0	88%	0%	6	0.730	0.200
Zethraeus 2002	Sweden	95	EQ-5D	72.0	88%	0%	9	0.760	0.180
Zethraeus 2002	Sweden	83	EQ-5D	72.0	88%	0%	12	0.760	0.200
Borgstrom 2006	Sweden	276	EQ-5D	69.5	91%	14%	4	0.820	0.010
Borgstrom 2006	Sweden	276	EQ-5D	69.5	91%	14%	12	0.860	0.010

Appendix 3B.4 Table 4: Characteristics of reviewed studies for post-wrist fracture

Studies	Countries	Sample size	HSUV elicitation method	Mean age	Female (%)	Recurrent fractures (%)	Time after fracture (months)	HSUV	Standard deviation of HSUV
Adachi 2010	International	4825	EQ-5D	68.7	100%	0%	NA	0.730	0.300
McDonough 2012	US	153	EQ-5D	68.1	72%	0%	NA	0.880	0.070
Borgstrom 2013	Austria	113	EQ-5D	67.9	92%	18%	4	0.760	0.217
Borgstrom 2013	Australia	50	EQ-5D	68.1	86%	12%	4	0.780	0.216
Borgstrom 2013	France	168	EQ-5D	68.4	90%	16%	4	0.700	0.198
Borgstrom 2013	Italy	30	EQ-5D	75.0	96%	7%	4	0.780	0.279
Borgstrom 2013	Russia	202	EQ-5D	62.6	86%	40%	4	0.810	0.218
Borgstrom 2013	Sweden	390	EQ-5D	69.2	92%	13%	4	0.830	0.202
Borgstrom 2013	USA	34	EQ-5D	69.3	82%	44%	4	0.680	0.268

HSUV, Health state utility value, HUI, Health utility index, SG, Standard gamble, VAS, Visual analogue scale

Chapter 4: Screening for and treatment of osteoporosis: construction and validation of a state-transition microsimulation cost-effectiveness model

4.1 Preface

This chapter documents an osteoporosis state-transition microsimulation model of osteoporosis-related fractures. Model validity is assessed in three facets: face, internal and external validity. This model is validated in the Chinese population, but is flexible enough to be adapted to other jurisdictions using country- and population-specific epidemiological and health economics data. It will be used as an important tool for researchers and policy makers to evaluate the cost-effectiveness of different osteoporosis screening and treatment strategies.

This chapter has been published in *Osteoporosis International* (Appendix 4A).

Impact factor: 4.17.

Si L, Winzenberg TM, Jiang Q, Palmer AJ. Screening for and treatment of osteoporosis: construction and validation of a state-transition microsimulation cost-effectiveness model. *Osteoporosis international*, May 2015. 26(5): 1477-89.

The published article of this chapter appears in an appendix to the chapter. It has been removed for copyright or proprietary reasons.

4.2 Abstract

Introduction: The objective of this study was to document and validate a new cost-effectiveness model of screening for and treatment of osteoporosis.

Methods: A state-transition microsimulation model using a lifetime horizon was constructed with seven Markov states (no history of fractures, hip fracture, vertebral fracture, wrist fracture, other fracture, post-fracture state and death) describing the most important clinical outcomes of osteoporotic fractures. Tracker variables were used to record patients' history, such as fracture events, duration of treatment, time-since-last-screening. The model was validated for Chinese post-menopausal women receiving screening and treatment versus no screening. Goodness-of-fit analyses were performed for internal and external validation. External validity was tested by comparing life expectancy, osteoporosis prevalence rate, lifetime and 10-year fracture risks with published data not used in the model.

Results: The model represents major clinical facets of osteoporosis-related conditions. Age-specific hip, vertebral and wrist fracture incidence rates were accurately reproduced (the regression line slope was 0.996, R^2=0.99). The changes in costs, effectiveness and cost-effectiveness were consistent with changes in both one-way and probabilistic sensitivity analysis. The model predicted life expectancy and 10-year any major osteoporotic fracture risk at the age of 65 of 19.01 years and 13.7% respectively. The lifetime hip, clinical vertebral and wrist fracture risks at age 50 were 7.9%, 29.8% and 18.7% respectively, all consistent with reported data.

Conclusions: Our model demonstrated good internal and external validity, ensuring it can be confidently applied in economic evaluations of osteoporosis screening and treatment strategies.

4.3 Introduction

Osteoporosis and osteoporotic fractures are of significant concern to patients and broadly to the society [1-3]. To date, several treatments are effective in preventing osteoporotic fractures [1]. However, the costs of osteoporotic fractures are substantial [4]. Osteoporosis challenges the sustainability of the healthcare system with rapidly ageing population in much of the world [2], making it essential to accurately assess the cost-effectiveness of different approaches to its prevention, screening and treatment.

Health economic evaluations are performed using randomized controlled trial data and/or using decision analytic modelling [5]. Evaluation solely based on randomized controlled trial (RCT) data is often limited to intermediate clinical endpoints and by short duration of follow-up that may not be long enough to capture all relevant health economics outcomes. As an alternative, health economic evaluations are performed with decision analytic modelling that extrapolates the RCT data to a longer period of follow-up.

Decision analytic modelling studies have been performed extensively in the field of osteoporosis in the past decades [6-13]. The quality of osteoporosis models has improved with time [10, 11], but inevitably they were constructed with some limitations due to use of less advanced modelling techniques or out-of-date input data [10]. The objective of this study was to develop and validate a new osteoporosis decision analytic model for the assessment of cost-effectiveness of osteoporosis screening and treatment strategies.

4.4 Methods

4.4.1 Model structure

This cost-effectiveness model is an individual-level state-transition model. Cost-effectiveness is analysed over a life-time horizon, but may be varied according to perspective. Both costs and effectiveness were discounted at 3% annually and were changeable according to country-specific pharmacoeconomic guidelines. The model had a 1-year cycle length and ran until death of simulated subjects. Construction and validation of the model were performed using TreeAge Pro Suite 2014 (TreeAge Software, Williamstown, Massachusetts).

Osteoporosis is a chronic disease with a number of consequences: patients simulated in the model are either alive or dead. Alive patients could stay without any fracture for the entire life

(represented as "no history of fracture"), or sustain a fracture (represented as "fractured"), or stay in post-fracture state (represented as "post-fracture"), or sustain another fracture (represented as "fractured"). Therefore a Markov approach was used in our model so as to be able to incorporate multiple disease states (*Figure 4.1*). Most fragility fractures occur in hip (proximal femur), vertebrae (spine) and wrist (distal radius), though they can occur in "other" sites such as humerus, pelvis, ribs and shoulder [14]. Accordingly, seven Markov states were included: no history of fractures, hip fracture, vertebral fracture, wrist fracture, other fracture, post-fracture state and death.

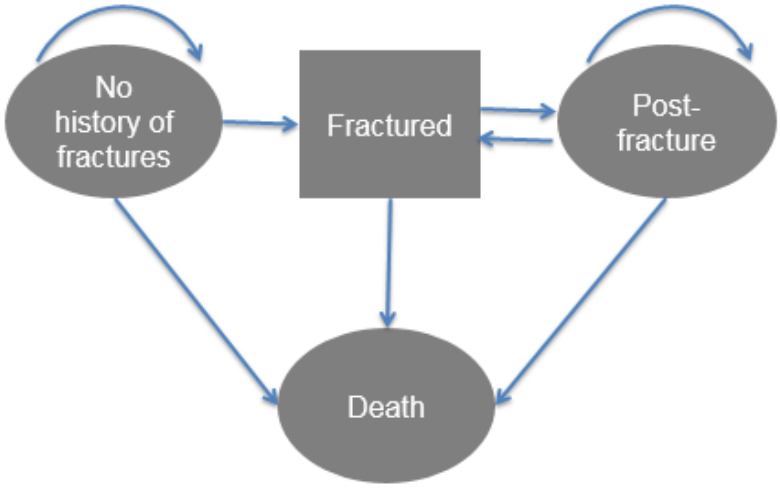

Figure 4.1. Structure of the Markov model. Simulated patients can transit between Markov states following the arrow direction, "Fractured" is a temporary state and denotes patients sustaining a hip, vertebral, wrist or other osteoporotic fracture. "Death" is an absorbing state that indicates all simulated patients will end in that state.

4.4.2 Model validation

The model validation procedure followed the recommendation from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force-7 [15] and three types of validities were addressed in our study: face validity, internal validity and external validity. Face validity is subjective and determined by clinicians who have an interest in the particular disease modelled. They are responsible for evaluating whether the model is constructed in accordance with best medical evidence. Internal validity is used to test any unintentional computational error and inconsistency with the model's specifications by comparing predicted values with input data. External validation compares the model's results with key outcomes from available published data [15].

For the internal validation, we modelled an osteoporosis screening strategy for Chinese post-menopausal women comparing its cost-effectiveness with that of no screening from the Chinese healthcare system perspective. A willingness to pay (WTP) threshold of $20,000 per quality-adjusted life year (QALY) gained was set to determine whether the intervention was cost-effective [16]. While for this example all the data inputs referred to published Chinese data for validation purposes, this can be varied to country- and ethnicity-specific data in future applications. The input epidemiological and health economic data are summarized *in Table 4.1.*

4.4.3 Bayes' revision

Screening could identify undiagnosed osteoporosis and therefore prevent future fractures by early treatment. However, as many screening techniques are not performed with perfect accuracy, sensitivity and specificity of the screening strategy were accounted for using Bayes' revision within the model structure. The Bayes' revision was characterized by Bayes' theorem which incorporates both prior and likelihood probabilities [17]. Revised posterior probabilities were adopted in the model using a built-in Bayes revision wizard in TreeAge Pro Suite 2014. Detailed calculations of posterior probability are elaborated in *Appendix 4B.1*.

4.4.4 Memory integration

In the model, whether a patient was screened was dependent on whether he/she sustained a fracture or was diagnosed with osteoporosis and whether he/she was between the rescreening intervals. Fracture risk depended on whether the fracture was the first fracture ever to have occurred, or a subsequent fracture following previous fractures. The effectiveness of medication (alendronate) depended on whether the patients persisted on treatment and whether they fully adhered to the recommended regimen. Subjects' health-state utility value (HSUV) depended on fracture sites and the time since fractures had occurred.

Tracker variables were used in our model to record patient characteristics. For example, "time after previous screening" and "fracture events" were used to determine whether the patient required a screening; "time after last fracture" and "time after diagnosis with osteoporosis" were used to determine the duration of treatment that contributed to determining medication persistence, adherence and offset time; "number of fractures" was used to determine the health-state utility value and costs for patients with multiple fractures. Individual patient-level (microsimulation) using tracker variables was implemented to account for these parameters.

Table 4.1 Key parameters in the model

Parameter	Base-case	Range for SA	Distribution	Source
Osteoporosis prevalence				
50-59 years	0.035	0.028-0.042 [a]	Triangular	[28]
60-69 years	0.142	0.114-0.170 [a]	Triangular	[28]
70-79 years	0.268	0.214-0.322 [a]	Triangular	[28]
80+ years	0.392	0.314-0.470 [a]	Triangular	[28]
Annual fracture incidence rate	Table 4.2	Table 4.2	-	
RR of wrist fracture in Asians versus Caucasians	0.72	0.53-1.00	Beta	[32]
Osteoporosis attribution probabilities for hip fractures				
50-64 years	0.75	0.20-0.85	Beta	[33]
65-84 years	0.85	0.50-0.95	Beta	[33]
85+ years	0.95	0.60-0.95	Beta	[33]
Osteoporosis attribution probabilities for vertebral fractures				
50-64 years	0.75	0.40-0.80	Beta	[33]
65-84 years	0.85	0.50-0.95	Beta	[33]
85+ years	0.95	0.60-0.95	Beta	[33]
Osteoporosis attribution probabilities for wrist fractures				
50-64 years	0.60	0.10-0.70	Beta	[33]
65-84 years	0.70	0.35-0.80	Beta	[33]
85+ years	0.70	0.55-0.90	Beta	[33]
Probability of nursing home residency after hip fractures				
60-69 years	0.04	0.032, 0.048 [a]	Triangular	[12]
70-79 years	0.04	0.032, 0.048 [a]	Triangular	[12]
80-89 years	0.12	0.096-0.144 [a]	Triangular	[12]
90+ years	0.17	0.136-0.204 [a]	Triangular	[12]
1-year mortality rate after hip fracture in nursing home residence				
60-69 years	0	0-0.02	Beta	[12]
70-79 years	0.13	0.104-0.156	Beta	[12]
80-89 years	0.22	0.176-0.264	Beta	[12]
90+ years	0.23	0.184-0.276	Beta	[12]
1-year mortality rate after hip fracture in community-dwelling				
60-69 years	0.04	0.032-0.048	Beta	[12]
70-79 years	0.06	0.048-0.072	Beta	[12]
80-89 years	0.11	0.088-0.132	Beta	[12]
90+ years	0.16	0.128-0.192	Beta	[12]
RR of death after vertebral fractures	1.82	1.52-2.17	Gamma	[39]
RR of death after wrist fractures	1.42	1.19-1.70	Gamma	[39]

Parameter	Base-case	Range for SA	Distribution	Source
RR of subsequent fracture following a prior fracture				
Hip fracture	2.0	1.9-2.2	Gamma	[12]
Vertebral fracture	2.0	1.6- 2.4	Gamma	[12]
Wrist fracture	1.9	1.6- 2.2	Gamma	[12]
RR of osteoporotic fracture with alendronate treatment				
Hip fracture without prior fracture	0.44	0.31-0.57	Beta	[36]
Hip fracture with prior fracture	0.49	0.34-0.64	Beta	[35]
Vertebral fracture without prior fracture	0.50	0.35-0.65	Beta	[36]
Vertebral fracture with prior fracture	0.53	0.37-0.69	Beta	[35]
Wrist fracture without prior fracture	0.88	0.62-1.00	Beta	[36]
Wrist fracture with prior fracture	0.52	0.36-0.68	Beta	[35]
Medication persistence				
First year after treatment onset	0.519	0.26-0.78 [b]	Triangular	[26]
Fifth year after treatment onset	0.182	0.09-0.27 [b]	Triangular	[6]
Treatment duration, years	5	2, 10	-	Assumption
Probability of being high adherent to alendronate [c]				
First year after treatment onset	0.619	0.31-0.93 [b]	Triangular	[27]
Third year after treatment onset	0.479	0.24-0.72 [b]	Triangular	[27]
Costs [d]				
Average direct costs of the first year after fractures [e]				
Hip fracture	6,462	3,231-9,693 [b]	Triangular	[41]
Vertebral fracture	4,884	2,442-7,326 [b]	Triangular	[41]
Wrist fracture	1,980	990-2,970 [b]	Triangular	[41]
Annual medication cost [f]	1,190	595-1,785 [b]	Triangular	[40]
DEXA scan	70	35-104 [b]	Triangular	[40]
Annual nursing home	4,395	3,767-5,023 [b]	Triangular	[42,43]
HSUVs				
Healthy/Osteoporotic population without fractures [g]				
60-64 years	0.728	0.582-0.874 [a]	Triangular	[45]
65-69 years	0.702	0.562-0.842 [a]	Triangular	[45]
70-74 years	0.685	0.548-0.822 [a]	Triangular	[45]
75-79 years	0.669	0.535-0.803 [a]	Triangular	[45]
80-84 years	0.655	0.524-0.786 [a]	Triangular	[45]
85+ years	0.643	0.514-0.772 [a]	Triangular	[45]
Hip fracture, first year [h]	0.776	0.720-0.844	Beta	[46]
Hip fracture, subsequent years [h]	0.855	0.800-0.909	Beta	[46]

Parameter	Base-case	Range for SA	Distribution	Source
Vertebral fracture, first year [h]	0.724	0.667-0.779	Beta	[46]
Vertebral fracture, subsequent years [h]	0.868	0.827-0.922	Beta	[46]
Wrist fracture, first year [h]	1.000	0.960-1.000	Triangular	[46]
Wrist fracture, subsequent years [h]	1.000	0.930-1.000	Triangular	[46]
Nursing home dwelling	0.400	0.320-0.480	Triangular	[12]
Annual discount rate				
Costs	0.03	0, 0.05	-	[16]
Effectiveness	0.03	0, 0.05	-	[16]

DEXA= dual-energy x-ray absorptiometry, RR = relative risk, SA = sensitivity analysis, HSUV = health-state utility value.

[a] One-way sensitivity analysis values ±20% of base-case value.

[b] One-way sensitivity analysis values ±50% of base-case value.

[c] Medication adherence is measured by medication possession ration MPR; MPR≥0.8 was defined as high compliance.

[d] Costs are presented in 2013 US dollars.

[e] Direct costs include costs of outpatient consultations, inpatient care, investigations, medication, rehabilitation after fracture events, physical therapy, transportation, homecare, preventive care foods and specific equipment.

[f] Annual costs of oral alendronate (70 mg per week) is $1,100, annual cost of calcium (600mg per tablet) and vitamin D_3 (125 IU per tablet) is $90.

[g] Visual analogue scale (VAS) HSUVs.

[h] Multipliers for the proportionate effects of fractures on HSUVs, calculated from Si. et al. [46].

4.4.5 Screening strategy

Screening with dual-energy X-ray absorptiometry (DEXA) and treatment with alendronate has been shown to be cost-effective in Caucasian contexts [7-9], therefore this was selected as the screening and treatment strategy in this study. In the "screening" arm, post-menopausal Chinese women aged 65 years without fracture history were assumed to be screened with DEXA. Diagnosis of osteoporosis was determined in accordance with World Health Organization (WHO) standards: i.e. hip (femoral neck) bone mineral density (BMD) 2.5 standard deviation (SD) or more below the young adult female mean (i.e. T-score ≤-2.5) [18]. Because DEXA scan at the femoral neck is currently regarded as the gold standard for osteoporosis diagnosis, we assumed a test sensitivity and specificity of 100% in the base-case analysis, with these values varied in extensive one-way sensitivity analysis [19]. It is recommended that follow-up bone densitometry should be performed at intervals greater than 2 years [20], therefore the rescreening time interval was set at 5-years for the base-case. A conceptual diagram of screening strategy versus no screening is illustrated in *Figure 4.2*.

4.4.6 Treatment

Oral alendronate, a cost-effective medication in the United Kingdom [21], was selected as the treatment option for patients identified has having osteoporosis in the screening arm, with the dosage of 70 mg per week with a combination of calcium and vitamin D_3. Those patients in the no screening arm were assumed to not receive alendronate treatment following a fracture. In the screening arm, patients with no osteoporosis were assumed to not receive any alendronate after a fracture. For patients identified as having osteoporosis in the screening arm received alendronate, and were assumed to continue on alendronate after a fracture occurred. The relative risks of fractures on alendronate therapy are shown in *Table 4.1*. Imperfect medication adherence and persistence affect cost-effectiveness of interventions [6], and their impact has been increasingly recognized in more recent osteoporosis health economics models [10]. Additionally, the residual effect on fracture risk for those who discontinue treatment was considered, known as offset-time effect [22, 23].

We used the definitions of medication adherence and persistence from ISPOR [24]. Medication compliance (synonym: adherence) refers to "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [24]. Percentage of doses taken as prescribed, known as medication possession ratio (MPR), was used to define the level of medication compliance [24]. An MRP ≥80% was defined as high compliance [25]. Medication persistence refers to "the duration of time from initiation to discontinuation of the therapy" [24].

Alendronate persistence data was not available for Asian populations so this was derived from Caucasian studies: 51.9% of those who commenced oral alendronate were assumed to discontinue in the first year [26], with the discontinuation rate assumed to decline linearly to 18.2% in the fifth year [6]. For those who stayed in treatment, we used medication adherence data from an Asian study. The probability of having high compliance was 61.9% at 12 months and decreased to 47.9% in the third year after treatment onset [27]. We assumed the residual effect would decline to "no effect" in a linear manner over 5 years after alendronate treatment discontinuation [9].

4.4.7 Osteoporosis prevalence

Age-specific prevalence rates of osteoporosis for the Chinese population was obtained from a recent meta-analysis [28], from which the initial distribution of the simulated patient population

was determined (e.g. at age 65, 85.8% no osteoporosis, 14.2% osteoporosis). After the initial stage, we calculated the probability of developing osteoporosis in people not having osteoporosis from the differences in prevalence of osteoporosis plus the mortality rate for that age band [28, 29]. The calculated risks of developing osteoporosis were 0.011, 0.014, 0.018 and 0.033 for ages 50-59, 60-69 70-79 and 80+ years respectively. We validated our calculation by comparing the model predicted age-specific osteoporosis prevalence rates against that from literature using cohort analysis. Similarly, the initial probability of simulated patients being osteoporotic in the "screening" arm was based on the prevalence rate, the probability of testing positive for those who were tested negative in the last screening was calculated from the prevalence rate, test sensitivity and mortality rate for that age band. Accordingly, the calculated risks of testing positive for individuals who did not have osteoporosis at the prior screening were 0.061, 0.084, 0.098 and 0.102 for ages 55-64, 65-74, 75-84, and 85+ years respectively.

4.4.8 Fracture rates and mortality

Annual fracture incidence rates were based on data from Chinese studies wherever available [30-32]. In the Chinese setting, there was limited data on "other" fracture incidence, therefore only hip, vertebral (clinical) and wrist fractures were included in the external validation analyses: annual age-specific hip fracture incidence rates were derived from the Hefei osteoporosis project [30], annual vertebral fracture incidence rates were taken from the Hong Kong Osteoporosis Study [31], annual wrist fracture incidence rates were taken from a Norwegian study and calibrated for Asian populations [32]. Fracture rates for patients with and without osteoporosis were adjusted from the age- and fracture site-specific proportion of osteoporosis attributed fractures, based on Melton's osteoporosis attributed rates approach [33]. Fracture site and age-specific annual incidence rates and adjusted annual osteoporotic fracture rates are presented in *Table 4.2*.

Patients in the model were allowed to sustain multiple fractures at different sites in different years of the simulation. The risk of subsequent fractures was higher for those with a fracture history [12, 34]. Accordingly, the efficacy of alendronate for both primary and secondary fracture prevention in osteoporotic patients was used, dependent on patient fracture history [35, 36]. The risk of hip fracture among poorly compliant patients was 35% higher than that in highly compliant patients [37], and there was a 17% increase for non-hip fracture in poorly compliant patients [38].

Age-specific mortality rates for the general population were obtained from the China Public Health Statistical Yearbook 2012 [29]. Mortality for the first year after hip fracture increased with age [12]. In the base-case analysis, patients who survived the first year after hip fracture were assumed either to reside in a nursing home post-fracture, remaining there for the rest of their life [12], or to normal community dwelling, dependent on the age at which the fracture was sustained. Patients were also assumed to have higher mortality rates following vertebral or wrist fracture events: the standardized mortality ratio (SMR) after vertebral fracture was 1.82 (95% CI: 1.52, 2.17) and SMR after wrist fracture was 1.42 (95% CI: 1.19, 1.70) [39].

4.4.9 Costs

Direct costs of screening tests, medical treatment, fracture inpatient costs and nursing home costs were based on published Chinese data [40-43]. All costs were converted to 2013 USD using a web-based currency converter [44]. As a Chinese healthcare system perspective was adopted in this model validation study, only direct costs after fractures were incorporated. We used data from a recent Chinese study on the economic burden of fractured patients with osteoporosis. Costs of outpatient consultation, inpatient, investigation, medication, rehabilitation after fracture events and physical therapy were included for direct medical costs [41]. Direct non-medical costs included costs of transportation, homecare, preventive care foods and specific equipment [41]. Average costs in the first year after hip, vertebral and wrist fracture were set at $6,462, $4,884 and $1,980 respectively [41]. Costs of treatment for those who tested positive were $1,190 ($1,100 for alendronate and $90 for calcium combined with vitamin D_3, 1000 mg calcium plus 125 IU vitamin D_3 per tablet) annually [40]. Costs of nursing home care varied between levels and geographical locations, and were assumed to be $4,395 *per annum* in the base-case analysis [42, 43]. No medication costs were assumed for patients who discontinued treatment, and a 30% reduction in medication costs was assumed for patients with poor adherence in the base-case analysis [6].

4.4.10 Health-state utility values (HSUVs)

The age-specific HSUVs for the female general population were retrieved from the National Health Services Survey 2008 [45]. HSUVs for women with osteoporosis but no history of fractures have been shown to be no different from those of the general population [46]. Subsequently, we defined HSUVs for osteoporotic women without fractures to be the same as those of the female general population. Hip and clinical vertebral fractures were associated with a decrease in HSUV, and the proportionate effect of a fracture on HSUV in the first and

subsequent year was calculated from a recent meta-analysis (*Table 4.1*) [46]. A HSUV multiplier of 0.4 was used for those residing in nursing homes after fractures [12].

4.4.11 Statistical methodology in internal and external validation

In the base-case analysis, distributions were sampled 100 times. After each sample, 2000 trials (patients) were run through the model using the values drawn from each sample. The mean costs and effectiveness following the 2,000 trials were then calculated. This process was repeated for each of the 100 samples, and the mean costs and effectiveness were calculated across each of the 100 samples x 2,000 trials, from which the mean ICER for the base-case was calculated. In one-way sensitivity analyses, only the mean value of one selected variable in the model was changed, while other variables remained the unchanged. Similar to the base-case analysis, we still considered the joint uncertainty across all variables. The statistical analysis used in the validation procedure followed that used by other long-term model validations [47-49]. For internal validity, the results generated from our model were compared with those from studies used in creating the model. Specifically, we compared age-specific hip, vertebral and wrist fracture annual incidence rates from model outputs against those from the reference studies. Goodness-of-fit was evaluated by plotting the model predictions versus observed data reported in the reference studies, fitting a linear curve through the points with the intercept of zero. The squared linear correlation coefficient (R^2), which was an index of the degree to which the paired measures co-vary, was provided using linear regression. External validation compared the model's results for key outcomes with available published data that was not used in the construction of the model [15], and goodness-of-fit was also evaluated using linear regression In this study, we compared the model's predictions of life expectancy (LE) and osteoporosis prevalence rates at specific ages, lifetime osteoporotic hip, clinical vertebral and all main (hip, clinical vertebral and wrist fracture combined) osteoporotic fracture risks, and 10-year fracture risks for all main osteoporotic fractures against the corresponding reported data [28, 31, 50-53]. All statistical analyses were performed using STATA (STATA 12.1, StataCorp LP, College Station, TX, USA).

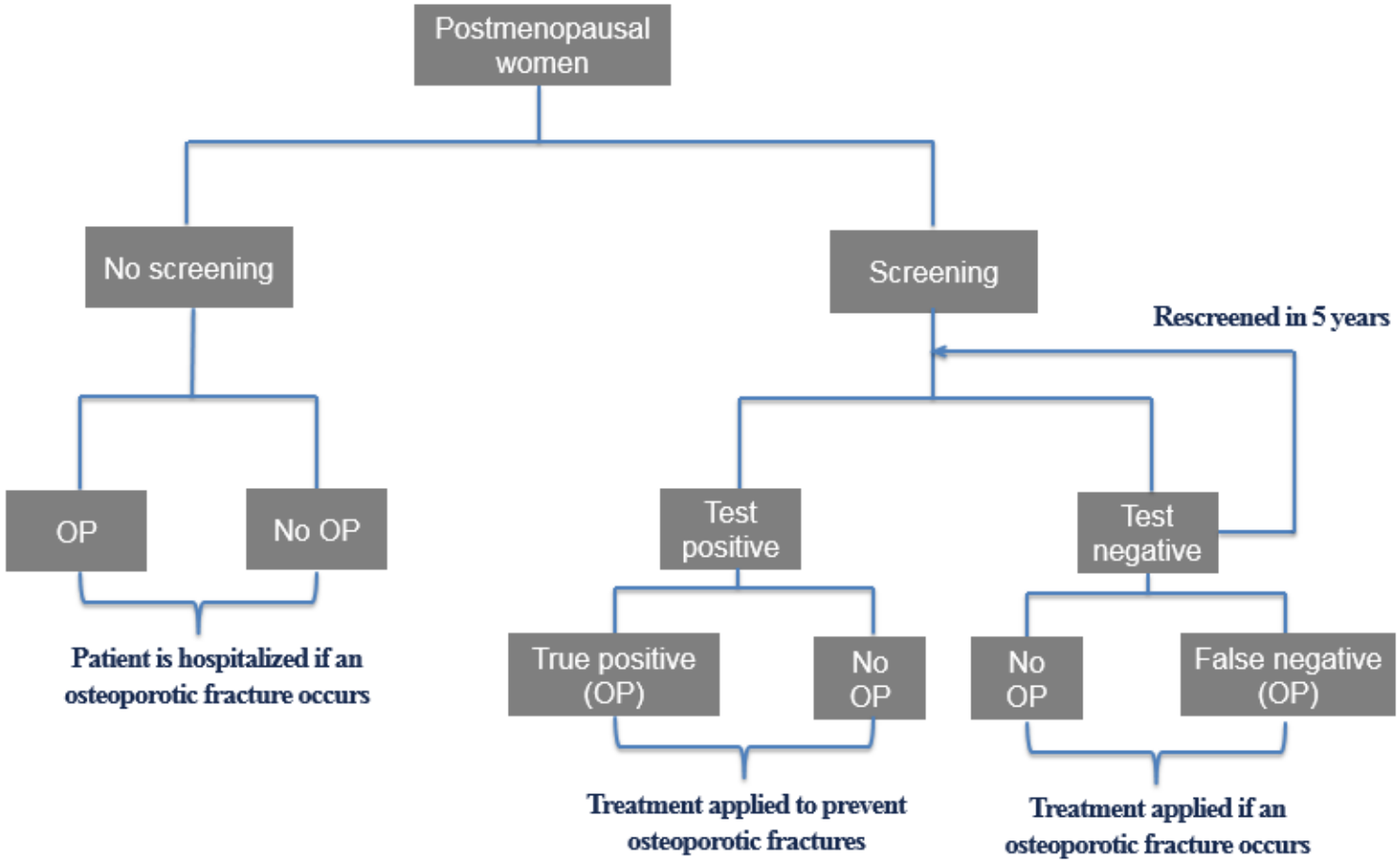

Figure 4.2 Conceptual diagram of the screening model. OP = osteoporosis. The model compares the screening strategy to no screening in postmenopausal women. Those subjects who tested positive in "Screening" arm are assumed to be treated with alendronate to prevent fractures. For those who tested negative in the last screening, a repeat screening is performed in 5 years.

Table 4.2 Age-specific annual fracture rates for total population and calculated annual fracture rates attributed from osteoporosis, per 1,000 person-years

Age (years)	Hip fracture [a]	Vertebral fracture [b]	Wrist fracture [c]
Annual fracture rates for total population			
50-54	0.33	2.19	4.76
55-59	0.46	3.13	7.32
60-64	0.54	5.16	11.16
65-69	0.96	5.64	12.95
70-74	2.33	8.74	13.17
75-79	4.08	12.05	13.87
80-84	6.44	21.19	15.01
85-89	6.59	26.89	15.10
90+	8.67	27.10 [d]	13.97
Calculated annual osteoporosis attributed fracture rates [e]			
50-54	7.20	47.76	60.06
55-59	6.50	44.21	60.43
60-64	4.08	38.97	49.72
65-69	4.94	29.01	39.04
70-74	8.96	33.60	28.83
75-79	12.68	37.45	23.87
80-84	16.97	55.84	21.32
85-89	15.97	65.17	19.41
90+	21.01	65.17	17.96

[a] Annual hip fracture rates for total population are derived from Wang et al. (2014) [30].

[b] Clinical vertebral fractures. Annual clinical vertebral fracture rates for total population are derived from Bow et al. (2012) [31].

[c] Wrist fracture incidences were derived for Caucasians from Lofthus et al (2008) [32], and in the model we were adapted the values to Asians by multiplying the relative risk of wrist fractures (0.72, 95% CI: 0.53-1.00) in Asians versus Caucasians.

[d] Calculated from original data using linear extrapolation.

[e] Osteoporosis attributed fracture risks were calculated using Melton's osteoporosis attributed rates (Melton et al. 1997 [33]).

4.4.12 Sensitivity analyses

One-way sensitivity analyses were performed to identify the influence of input parameters on the outcomes. Sensitivity and specificity of DEXA for diagnosing osteoporosis, osteoporosis prevalence rate, annual fracture risks, treatment efficacy and HSUVs were varied by ±20% of the values used in the base-case analysis. Medication persistence and probability of being highly adherent, probability of individuals residing in a nursing home after a hip fracture, inpatient costs for hip, vertebral and wrist fractures, annual medication costs and costs of screening were varied by ±50% of the values used in the base-case analysis [54]. Additionally, we performed one-way sensitivity analyses by assuming different discount rates on cost and

effectiveness, treatment duration, no offset time effect after medication discontinuation and different screening initiation age. As some variables were defined by a mean and standard error, distributions were applied in the model. Probabilistic sensitivity analysis was performed, in which sampling of distributions of input parameters was performed to address the uncertainties around multiple parameters simultaneously [54]. Cost-effectiveness acceptability curves were generated to visually illustrate the probabilities of screening and appropriate treatment being cost-effective.

4.5 Results

4.5.1 Face validity and internal validation

The model was designed and constructed by both experienced clinicians (Andrew Palmer, Tania Winzenberg) and health economics experts (Lei Si, Andrew Palmer). From a clinical perspective, the model structure was determined to correctly represent all important clinical facets of osteoporosis screening and fractures [10].

We performed a total of 27 internal validations by comparing model predictions of age-specific hip, clinical vertebral and wrist fracture incidence rates against those data used in creating our model. The results generated by the model closely match the published data from which the input probabilities were derived: the regression line slope was 0.996, which was close to 1.00, and the R^2 was 0.99 which indicated that the model faithfully reproduced the published data. The collective results for the internal validation are shown in *Appendix 4B.2.*

Table 4.3 summarizes the costs, effectiveness and the incremental cost-effectiveness ratio (ICER) of screening with DEXA versus no screening. The mean costs for screening and no screening were $1,939 and $1,619 respectively for the base-case analysis, the respective mean QALYs were 9.9442 and 9.722. The cost per QALY gained for screening versus no screening was $1,440 in the base-case analysis.

4.5.2 Sensitivity analyses

Without discounting for costs and effectiveness, the cost per QALY gained decreased to $931. The ICER increased to $1,844 when costs and effectiveness were discounted by 5% annually.

The accuracy of the screening test also impacted on outcomes: lower test sensitivity and specificity yielded higher costs but lower effectiveness for the screening strategy while the costs and effectiveness of no screening remained unchanged.

Medication persistence and adherence both impacted on the ICER: costs per QALY gained decreased with lower and increased with higher medication persistence and adherence. Costs and effectiveness did not change in the no screening group because no alendronate treatment was assumed for individuals in the no screening group. Effectiveness in the screening arm changed only slightly compared to that in the base-case analysis, whereas average costs changed more substantially especially with varied medication persistence.

Costs of fracture and screening did not impact on ICER significantly: costs per QALY gained were all higher than the WTP threshold and close to that in the base-case analysis. However, annual medication cost had a dramatic impact on the cost-effectiveness of DEXA screening: with a 50% decrease of annual medication cost, the DEXA screening was cost-saving compared with no screening.

Costs per QALY gained were $3,347, if screening was initiated at the age of 60 DEXA screening was cost-saving if the screening was initiated at the age of 70 years. The cost-effectiveness acceptability curves (CEAC) were provided showing the probabilities of screening being cost-effective given a continuous WTP threshold (*Figure 4.3*). Given the WTP of $20,000 per QALY gained, screening initiated from age 65years had a probability of 99% of being cost-effective.

Table 4.3 Summary of costs, effectiveness, ICER of DEXA screening versus no screening strategy: base-case and one-way sensitivity analyses

Parameters	Costs [a]		Effectiveness [b]		ICER
	DEXA	No screening	DEXA	No screening	
Base-case	1,939	1,619	9.944	9.722	1,440
One-way sensitivity analyses					
Discount rates: 0%	2,922	2,545	12.972	12.567	931
Discount rates: 5%	1,542	1,252	8.584	8.427	1,844
1.2 times base case annual fracture risks	2,136	1,905	9.881	9.615	870
0.8 times base case annual fracture risks	1,724	1,320	10.006	9.832	2,314
1.2 times base case treatment efficacy	1,915	1,619	9.950	9.722	1,290
0.8 times base case treatment efficacy	1,963	1,619	9.937	9.722	1,598
Treatment duration: 2 years	1,818	1,619	9.937	9.722	925
Treatment duration: 10 years	1,967	1,619	9.945	9.722	1,566
No treatment offset time effect [c]	1,981	1,619	9.930	9.722	1,736
0.8 times base case DEXA sensitivity	2,403	1,619	9.887	9.722	4,751
0.8 times base case DEXA specificity	4,524	1,619	9.918	9.722	14,795
1.5 times base case medication persistence [d]	2,179	1,619	9.948	9.722	2,472
0.5 times base case medication persistence [d]	1,689	1,619	9.934	9.722	328
1.5 times base case medication adherence [e]	1,961	1,619	9.947	9.722	1,514
0.5 times base case medication adherence [e]	1,915	1,619	9.939	9.722	1,357
1.5 times base case probability of nursing home	1,972	1,670	9.942	9.719	1,355
0.5 times base case probability of nursing home	1,906	1,570	9.946	9.724	1,522
1.5 times base case fracture inpatient costs	2,401	2,377	9.944	9.722	112
0.5 times base case fracture inpatient costs	1,476	862	9.944	9.722	2,768
1.5 times base case annual medication costs	2,314	1,619	9.944	9.722	3,133
0.5 times base case annual medication costs	1,563	1,619	9.944	9.722	cost-saving
1.5 times base case screening cost	2,039	1,619	9.944	9.722	1,892
0.5 times base case screening cost	1,839	1,619	9.944	9.722	988
1.5 times base case nursing home annual cost	1,969	1,672	9.944	9.722	1,343
0.5 times base case nursing home annual cost	1,908	1,567	9.944	9.722	1,537
1.2 times base case HSUVs	1,939	1,619	11.954	11.720	1,365
0.8 times base case HSUVs	1,939	1,619	7.941	7.744	1,625
Screening population aged 60 years	2,245	1,590	11.706	11.510	3,347
Screening population aged 70 years	1,603	1,637	8.186	7.932	cost-saving

ICER = incremental cost-effectiveness ratio, DEXA = dual-energy x-ray absorptiometry, HSUV = Health-state utility value

[a] Costs are lifetime direct costs and presented in 2013 US dollars.

[b] Effectiveness is presented in quality-adjusted life year (QALY).

[c] Medication offset time effect refers to the residual effect on fracture risks after the discontinuation of treatment.

[d] Medication adherence remains unchanged.

[e] Medication persistence remains unchanged.

4.5.3 External validation

The prediction of life expectancy (LE) for 65 year old women without screening was 19.01 years and 15.74 years for women aged 69 years (average: 17.38 years). Our model prediction was similar to the World Health Organization (WHO) audit whereas the mean LE for Chinese women aged 65-69 years is 17.15 years [53]. Osteoporosis prevalence rates for ages 60-69, 70-79 and 80+ years and older were predicted at 14.4%, 26.3% and 39.9% respectively, closely matching the respective prevalence rate from the literature of 14.2%, 26.8% and 39.2% [28]. Our model predicted the lifetime osteoporotic hip, clinical vertebral and wrist fracture risks for Chinese women aged 50 years to be 7.9% (95% CI: 7.2%, 8.6%), 29.8% (95% CI: 27.8%, 31.9%) and 18.7% (95% CI: 17.2%, 20.1%) respectively. The lifetime risk of all osteoporosis-related fractures for Chinese women aged 50 years was predicted to be 56.3% (95% CI: 52.1%, 60.6%). The predictions were comparable to the corresponding values from a Korean study, where residual lifetime risk for hip, distal radius and all osteoporotic fractures were reported as 12.3%, 21.7% and 59.5% respectively [52]. These predictions were consistent with the results of a study on fracture risk across different ethnicities, in which the hip fracture rate for Asian women was estimated to be less than half that of Caucasians, but the vertebral fracture rate was higher in Asians than Caucasians [31]. The residual lifetime hip, clinical vertebral and any common osteoporotic fracture risks in a Caucasian population at age 50 years were estimated at 23%, 15% and 46% respectively [50]. By setting the simulation initiation age at 65 years, the 10-year risk of any major osteoporotic fractures (i.e. hip, clinical vertebral and wrist fractures) was predicted to be 13.7% (95% CI: 12.5%, 15.2%), which is comparable to the value of 17% observed in a Hong Kong population aged 65 years and older with a total hip BMD T-score $\leq$-2.5 [51]. The regression line slope was 0.952, which was close to 1.00, and the R^2 was 0.994. The collective results for the external validation are shown in *Appendix 4B.2*.

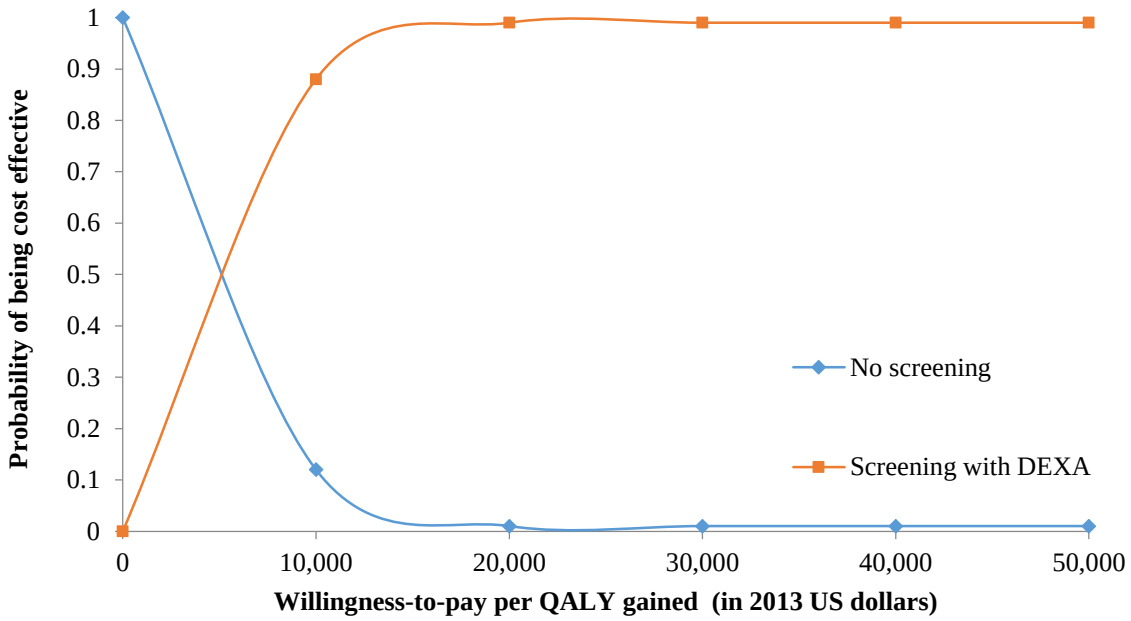

Figure 4.3 Cost-effectiveness acceptability curves of screening initiated from age 65 years at different levels of willingness-to-pay (WTP) per quality-adjusted life year (QALY) gained versus no screening. Given the WTP threshold of $20,000 per QALY gained, the probability of screening being cost-effective versus no screening is 99% if screening is initiated at age 65 years.

4.6 Discussion

The application of health technology assessment has increased remarkably over the past decades and is expected to grow in the future [10, 11]. A successful health analytic model should be acceptable to healthcare providers, health policy decision makers and healthcare payers. Moreover, it should be transparent and validated against real-life data [47]. Our osteoporosis model was constructed using updated epidemiological and economic data. The model structure and functionality has been documented, and the validation analyses revealed the accuracy of reproduction of input data. Moreover, our model was constructed independently, without bias to any specific medication, intervention, or funding body, avoiding the implicit inherent bias potentially associated with external funding. The flexibility and adaptability of the model was considered throughout the model construction process. The model can be used for evaluating the costs, effectiveness and cost-effectiveness of screening for, prevention and medical treatment of osteoporotic fractures. It was designed not only for economic evaluations for primary fracture prevention (i.e. prevention of a first osteoporotic fracture) but can also be adapted for secondary fracture prevention (i.e. preventions targeted at the population who have already sustained a fracture). Further, it was not restricted to a specific

country or ethnic population, but can be applied to different populations and countries with population- and country-specific data. The model was constructed in TreeAge software which is widely used in cost-effectiveness modelling studies. In the future, a user-friendly web-based interface will make the model publically available. Finally, the R^2 values are all close to 1 for the internal and external validations, which indicates our model has good internal and external validity: the R^2 values are even greater than some validated cost-effectiveness models that have been extensively used to assist the submissions of new pharmaceutical products for reimbursement around the world such as CORE diabetes model (R^2=0.9574 for the internal validation and R^2=0.9023 for the external validation) [47] and the Archimedes diabetes model (R^2=0.99 for the external validation) [48].

Medication adherence and persistence have consistently been found to impact on medication effectiveness and healthcare costs, as well as cost-effectiveness of health interventions [6, 25, 55, 56]. In our study, we confirmed the previous findings in terms of the substantial impact on cost-effectiveness of osteoporosis screening (*Table 4.3*). However, the change of effectiveness in screening strategy was relatively small in one-way sensitivity analyses. The reasons are two-fold: first, this study incorporated screening of the whole population of both osteoporotic and non-osteoporotic people, therefore the changes in medication adherence impacted only to a minor degree on effectiveness, as most of the simulated individuals were non-osteoporotic at baseline. This differs from the findings reported in a cost-effectiveness study of fracture preventions where all simulated patients were osteoporotic [56]. In that Belgian study, medication non-adherence decreased the effectiveness (expressed in QALY gained) by 59% comparing with the full adherence scenario [56]. In another study of the cost-effectiveness of screening a Belgian population, effectiveness of the screening strategy with real-world medication adherence only decreased 0.34% from that with full adherence (12.95 QALY gained for real-world adherence and 13.00 QALY gained for full adherence compared with no screening) [6]. Second, impact of poor medication adherence and persistence was offset by residual medication effects after treatment discontinuation. Assuming no offset time effects, the effectiveness of screening decreased by 0.014 QALY compared to the base-case analysis (*Table 4.3*). These results further demonstrate the importance of accounting for medication adherence and persistence in health economic evaluations of osteoporosis management strategies.

To date, several models have been constructed and used in the field of screening for- and

treatment of osteoporosis [7-9, 13, 49, 57-59]. Other than Mueller's model, all models were patient-level (microsimulation) based. Most of models were of good quality and satisfied the recommendations from a recent systematic review with regard to the progression of osteoporosis models [10]. Nevertheless, limitations existed in these models. For example, rescreening intervals for patients diagnosed as non-osteoporotic in the last screening were not considered in Mueller's model [8, 58]; medication adherence and offset time effects were not considered in the model from Nshimyumukiza [59]; medication persistence was not included in Kingkaew's model [13]. Medication persistence, adherence and offset time are recommended to be incorporated in osteoporosis models due to the demonstrated impact of these parameters on the cost-effectiveness of osteoporosis interventions [6, 10]. In the model from Hiligsmann [6], medication persistence and adherence was considered in the "screening and treating" arm but not in the "no intervention" arm.

There are a number of major strengths to our modelling approach. First, Bayes' revision was adopted in our model structure, which calculated the posterior probabilities using prior and likelihood probabilities. Bayes' revision has not been adopted in previous screening models for osteoporosis but is recommended [6, 7, 9, 13, 60]. Second, the model used patient-level (microsimulation) techniques rather than cohort analysis. Microsimulation models using a lifetime horizon account for the evolution of patient characteristics over time, such as fracture history, time since treatment initiation and time since fracture, and are therefore preferred by healthcare decision makers [61]. Third, medication adherence, persistence and offset time effect were all thoroughly accounted for in the model.

There are potential limitations to our model. First, adverse events (i.e. events from the medication side effects) were not recorded. Side effects of alendronate such as gastrointestinal adverse events and osteonecrosis of the jaw were not included because the health-state utility impact of adverse events is unclear, and skeletal side effects occur rarely at the doses used in osteoporosis treatment [62-64]. However, medication adverse events should ideally be considered in health economic evaluation on medications when good epidemiological data are available on such adverse events. Second, our model assumed a fixed rescreening interval for those not diagnosed with osteoporosis. Several organizations provided different recommendations that varied from at least six months to 5 years [20, 65, 66]. Recent studies suggest that the interval of repeat BMD testing should be determined by age, the patient's clinical risk factors as well as baseline bone density [67-69]. With limited prospective data,

frequency of bone densitometry is controversial. Our study used a 5-year rescreening interval in the base-case analysis and was varied in sensitivity analysis, we expect to adopt a flexible rescreening interval in the future when country-specific clinical trial data are available. Third, patients in the "no screening" arm who sustained an osteoporotic fracture ideally should be prescribed medication to prevent subsequent fractures. However, the current pattern of secondary fracture prevention is unknown in China, therefore we only assumed inpatient costs one year after fracture in the "no screening" arm. Finally, because of the paucity of data on "other fractures" in Chinese studies, we were unable to validate our "other fracture" rates generated by the model against published Chinese data. In addition, some of the data we used in this study were from Caucasian populations, such as the probability of residing in a nursing home after a hip fracture, and treatment efficacy. Future external validation and updates of the model are expected when new evidence becomes available.

Osteoporosis models have been used extensively in cost-effectiveness studies on osteoporosis since the first model was published in 1980 [70]. Good cost-effectiveness models are expected to be consistent with a coherent theory of the objective health condition [71], so that the structure should represent all important disease outcomes and the transition parameters should be consistent with the most convincing evidence from clinical trials or meta-analyses. Evolution in osteoporosis model structures over time is possibly a reflection of the adoption and implementation of good practice in modelling studies. Microsimulation models are preferable over cohort based models, which lack comprehensive memory integrity, but they require more sophisticated data from clinical trials. Many of the previous models estimated the specificity and sensitivity of the screening approach by relying on bone mineral densitometry without incorporating other clinical risk factors such as history of fracture, glucocorticoids use and smoking. Clinical risk factors were found to contribute substantially to the risk of fracture and were included in many fracture risk models such as FRAX [72]. FRAX not only incorporated BMD at the femoral neck but other clinical risk factors as an indicator of medication intervention threshold. However, the recommended intervention threshold is not applicable to the Chinese population [73, 74]. Our model is able to include these assessment tools and we would like to define the threshold for the Chinese population from a health economic perspective when relevant epidemiological data are available. With multiple osteoporosis models developed around the world, and the ongoing evolution of modelling techniques, osteoporosis health economics computer modellers should be encouraged to meet regularly to compare their models against each other and against data from clinical trials and

other high quality studies and to optimize the future development of modelling techniques. This approach has been successful in cross-validation and improvement of models in other disease areas, e.g.: the Mount Hood Challenge series in diabetes modelling to compare model projections with the best available clinical and epidemiological outcomes and to discuss avenues of research to improve future models [75-77]. It is recommended that a similar series of meetings in the field of osteoporosis health economics modelling should be established.

A new cost-effectiveness state-transition microsimulation model of screening for and treatment of osteoporosis was constructed that implements a unique combination of modern-day modelling techniques. It is a flexible model with good internal and external validity that closely reproduces clinical input data and epidemiological studies. This new model provides an important tool for researchers and policy makers to test the cost-effectiveness of osteoporosis screening and treatment strategies. Nevertheless, further external validation and updates of the model will constantly be needed as new evidence and more advanced modelling techniques become available.

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Appendix 4B.1: Bayes' revision in decision trees

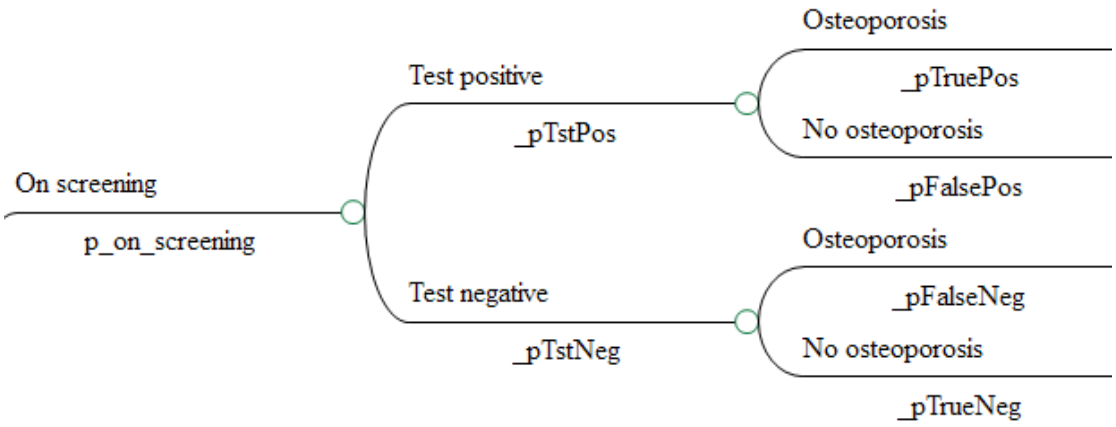
It is recommend to use Bayes' revision in models that incorporate imperfect tests or forecasts. In this study context, bone densitometry may not able to detect all osteoporotic patients therefore Bayes' revision is employed in the decision tree – as DEXA at the femoral neck is the gold standard for diagnosing osteoporosis [18], we assumed sensitivity and specificity of 100% [19], but carried this assumption in one-way sensitivity analyses.

The Bayes' revision allowed the calculation of posterior (or decision) probabilities by the following formula:

$$\mathrm{P(Posterior)} = \frac{\mathrm{P(Evidence|Hypothesis)} \times \mathrm{P\ (Hypothesis)}}{\mathrm{P\ (Evidence)}}$$

Where P(Hypothesis) is called a prior probability and P(Evidence) is called a marginal probability.

In our sub-decision-tree, there are 4 posterior probabilities incorporated in "On screening" arm: P(true positive, i.e. osteoporotic patients who are tested positive), P(false positive, i.e. healthy people who are tested positive), P(true negative, i.e. healthy patients who are tested negative), P(false negative, i.e. osteoporotic patients who are tested negative).



The posterior probabilities are calculated from the formulas bellow:

$$\mathrm{P(TruePos)} = \frac{\mathrm{P(Osteoporosis)} \times \mathrm{Sensitivity}}{\mathrm{P(Osteoporosis)} \times \mathrm{Sensitivity} + (1 - \mathrm{P(Osteoporosis)}) \times (1 - \mathrm{Specificity})}$$

$$\mathrm{P(FalsePos)} = \frac{(1 - \mathrm{P(Osteoporosis)}) \times (1 - \mathrm{Specificity})}{\mathrm{P(Osteoporosis)} \times \mathrm{Sensitivity} + (1 - \mathrm{P(Osteoporosis)}) \times (1 - \mathrm{Specificity})}$$

$$\mathrm{P(TrueNeg)} = \frac{(1 - \mathrm{P(Osteoporosis)}) \times \mathrm{Specificity}}{\mathrm{P(Osteoporosis)} \times (1 - \mathrm{Sensitivity}) + (1 - \mathrm{P(Osteoporosis)}) \times \mathrm{Specificity}}$$

$$\mathrm{P(FalseNeg)} = \frac{\mathrm{P(Osteoporosis)} \times (1 - \mathrm{Sensitivity})}{\mathrm{P(Osteoporosis)} \times (1 - \mathrm{Sensitivity}) + (1 - \mathrm{P(Osteoporosis)}) \times \mathrm{Specificity}}$$

Appendix 4B.2: Internal and external validation

Internal validation

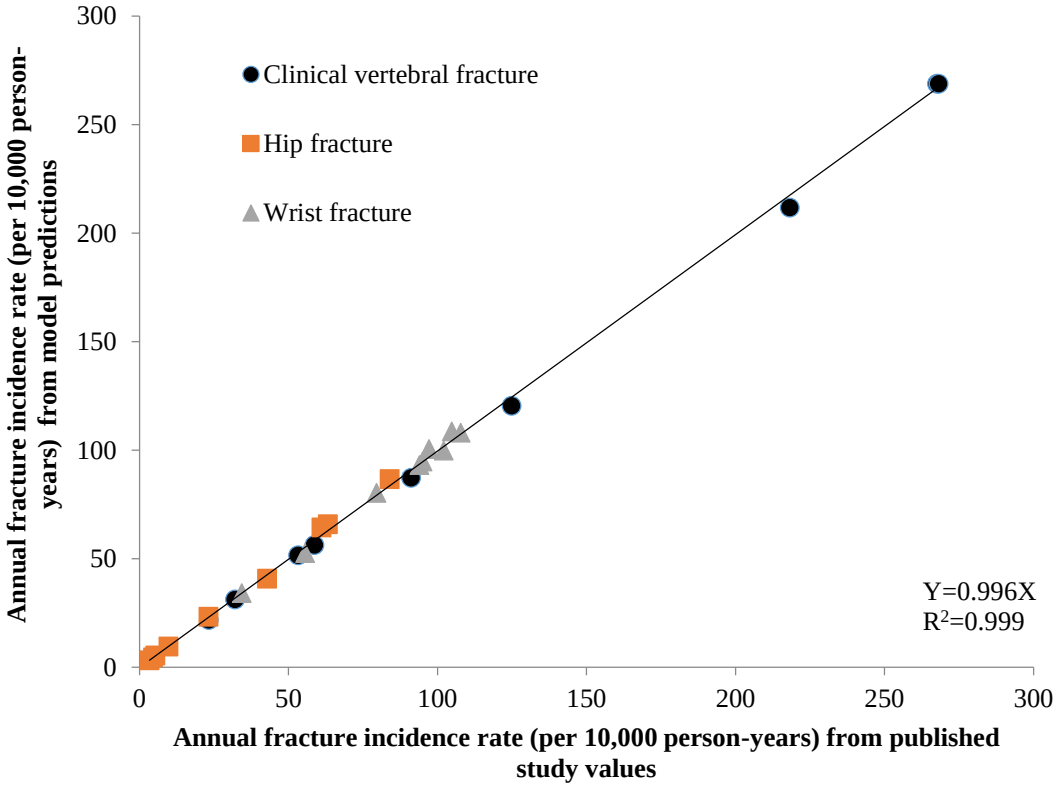
For internal validity, the results generated by our model were compared with those reported from studies used in creating the model. Specifically, we compared age-specific hip, vertebral and wrist fracture incidence rates from model outputs against those from the reference studies. Goodness of fit was evaluated by plotting the model predictions versus observed data reported in the reference studies, fitting a linear curve through the points with the intercept of zero. The squared linear correlation coefficient (R^2), which is an index of the degree to which the paired measures co-vary was provided using linear regression.

Appendix 4B.2 Table 1. Annual fracture rates, per 10,000 person-years from model reproduction and model inputs

Age (years)	Annual fracture rates, per 10,000 person-years from model prediction	Annual fracture rates, per 10,000 person-years from literature
Hip fracture		
50-54	3.4	3.3
55-59	4.6	4.6
60-64	5.3	5.4
65-69	9.7	9.6
70-74	23.2	23.3
75-79	42.8	40.8
80-84	61	64.4
85-89	63.2	65.9
90+	84	86.7
Clinical vertebral fracture		
50-54	23.2	21.9
55-59	32.1	31.3
60-64	53.3	51.6
65-69	58.7	56.4
70-74	91.1	87.4
75-79	124.9	120.5
80-84	218.2	211.9
85-89	267.7	268.9
90+	268.2	268.9
Wrist fracture		
50-54	34.3	34.272
55-59	55.6	52.704
60-64	79.55	80.352
65-69	93.9	93.24
70-74	94.95	94.824
75-79	102.05	99.864
80-84	107.8	108.072
85-89	104.8	108.72
90+	97.15	100.584

In total, we performed 27 internal validations by comparing model prediction of age-specific hip, clinical vertebral and wrist fracture incidence rate against those used as model inputs (*Appendix 4B.2 Table 1*).

According to the values in *Appendix 4B.2 Table 1*, goodness-of-fit test is illustrated in *Appendix 4B.2 Figure 1*, by plotting the model predictions versus observed data, the regression line slope was 0.996 which was close to 1.00 and the R^2 was 0.99 which indicated that the model faithfully reproduced the published data.



Appendix 4B.2 Figure 1. Goodness-of-fit test for model internal validation

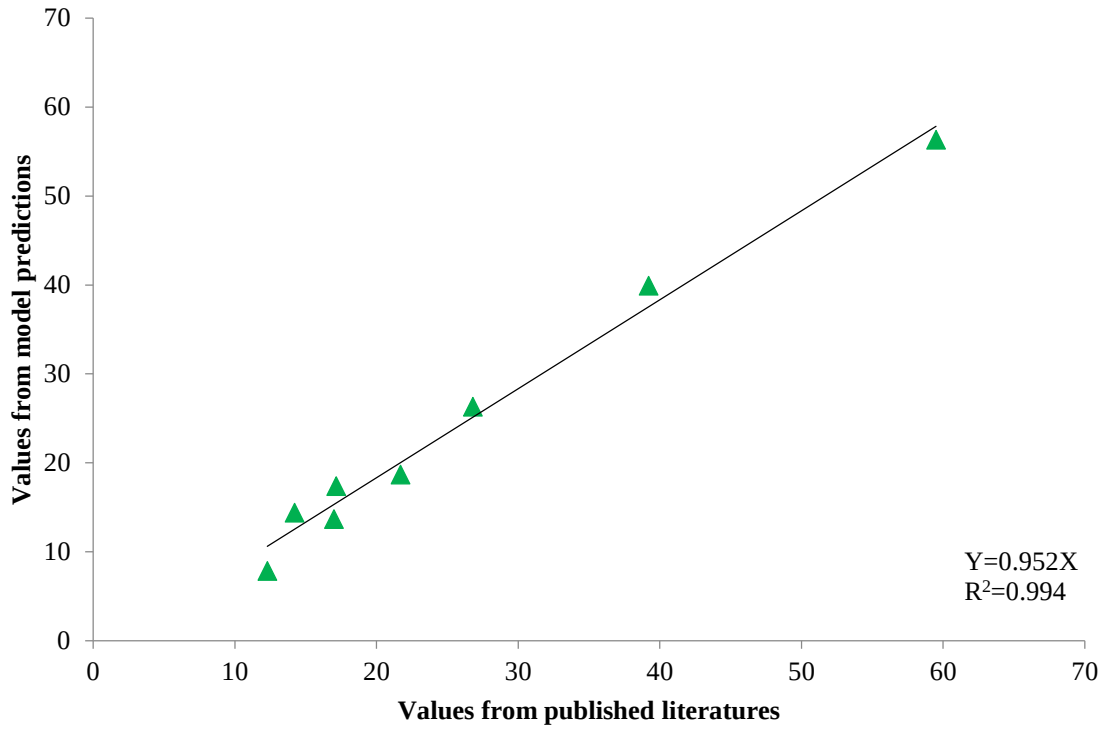
External validation

Similar to the internal validation, goodness-of-fit test was performed using linear regression. We compared the model's predictions of life expectancy (LE) and osteoporosis prevalence rates at specific ages, lifetime osteoporotic hip, clinical vertebral and all main (hip, clinical vertebral and wrist fracture combined) osteoporotic fracture risks, and 10-year fracture risks for all main osteoporotic fractures against the corresponding reported data (*Appendix 4B.2 Table 2*).

According to the values in *Appendix 4B.2 Table 2*, goodness-of-fit test is illustrated in *Appendix 4B.2 Figure 2*. The regression line slope was 0.952, which was close to 1.00, and the R^2 was 0.994.

Appendix 4B.2 Table 2. External validation: comparison of model predictions to the published data

Parameters	Model predictions	Data from literature
Life expectancy for age 65-69, years	17.15	17.38
Prevalence of osteoporosis ,%		
60-69 years	14.2	14.4
70-79 years	26.8	26.3
80+ years	39.2	39.9
Lifetime osteoporotic fracture risk at age 50 years, %		
Hip fracture	12.3	7.85
Wrist fracture	21.7	18.68
Any major fracture (Hip, clinical vertebral and wrist fractures)	59.5	56.31
10-year risk of any major osteoporotic fractures (Hip, clinical vertebral and wrist fractures), %	17	13.69



Appendix 4B.2 Figure 2. Goodness-of-fit test for model external validation

Chapter 5: Residual lifetime and 10-year absolute risks of osteoporotic fractures in Chinese men and women

5.1 Preface

Residual lifetime risk describes the cumulative risk of developing a disease over the remaining lifetime. Assessing residual lifetime fracture risks provides information of absolute risks on the population level and potential clinical burden of disease. This chapter documents the first application study using our osteoporosis health economic model, residual lifetime and 10-years osteoporotic fracture risks for Chinese women and men aged 50 years and above are estimated. More than two fifths of Chinese women and around one tenth of Chinese men aged 50 years are expected to sustain a first osteoporotic (hip, clinical vertebral or wrist) fracture in their remaining lives. While fracture risk estimates are lower in Chinese than Caucasian populations, it is clear that osteoporotic fractures will still result in a major burden for the Chinese health system and the prevention of osteoporosis is an issue which requires serious attention.

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The published article of this chapter appears in an appendix to the chapter. It has been removed for copyright or proprietary reasons.

5.2 Abstract

Objective: To determine the residual lifetime and 10-year absolute risks of osteoporotic fractures in Chinese men and women.

Methods: A validated state-transition microsimulation model was used. Microsimulation and probabilistic sensitivity analyses were performed to address the uncertainties in the model. All parameters including fracture incidence rates and mortality rates were retrieved from published literatures. Simulated subjects were run through the model until they died to estimate the residual lifetime fracture risks. A 10-year time horizon was used to determine the 10-year fracture risks. We estimated the risk of only the first osteoporotic fracture during the simulation time horizon.

Results: The residual lifetime and 10-year risks of having the first osteoporotic (hip, clinical vertebral or wrist) fracture for Chinese women aged 50 years were 40.9% (95% CI: 38.3-44.0%) and 8.2% (95% CI: 6.8-9.3%) respectively. For men, the residual lifetime and 10-year fracture risks were 8.7% (95% CI: 7.5-9.8%) and 1.2% (95% CI: 0.8-1.7%) respectively. The residual lifetime fracture risks declined with age, whilst the 10-year fracture risks increased with age until the short-term mortality risks outstripped the fracture risks. Residual lifetime and 10-year clinical vertebral fracture risks were higher than those of hip and wrist fractures in both sexes.

Conclusions: More than one third of the Chinese women and approximately one tenth of the Chinese men aged 50 years are expected to sustain a major osteoporotic fracture in their remaining lifetimes. Due to increased fracture risks and rapidly ageing population, osteoporosis will present a great challenge to the Chinese healthcare system.

Limitations: While national data was used wherever possible, regional Chinese hip and clinical vertebral fracture incidence rates were used, wrist fracture rates were taken from a Norwegian study and calibrated to the Chinese population. Other fracture sites like tibia, humerus, ribs and pelvis were not included in the analysis, thus these risks are likely to be underestimates. Fracture risk factors other than age and sex were not included in the model. Point estimates were used for fracture incidence rates, osteoporosis prevalence and mortality rates for the general population.

5.3 Introduction

Osteoporotic fractures contribute a substantial disease burden worldwide, resulting in increased mortality and quality of life reduction [1, 2], especially in older populations. China has one of the most rapidly ageing populations: the proportion of the elderly in China is projected to be a quarter of its total population by 2050 [3]. Inevitably, the rising disease and economic burden of osteoporotic fractures will challenge the sustainability of the Chinese healthcare system [4].

Estimations of residual lifetime and 10-year osteoporotic fracture risks provide important information to healthcare policy makers, as they may ration scarce healthcare resources according to the future burden of disease. Residual lifetime and 10-year osteoporotic fracture risks have been widely reported for Caucasian populations [5-8], but very limited studies have been performed in Asian populations [9, 10], and only one [11] in the Chinese population. Because life expectancy and fracture rates in the Chinese population have increased in the past decade [12, 13], updated estimates of hip fracture are required as well of estimates of risk for other important sites begin needed. Moreover, accurate projections of residual lifetime and 10-year vertebral and wrist fracture risks for the Chinese population will allow international comparisons.

The objective of this study was to determine the residual lifetime and 10-year absolute risks of major osteoporotic fractures (hip, clinical vertebral and wrist fractures) in Chinese men and women aged 50 years to 90 years.

5.4 Methods

5.4.1 Health economics model overview

A validated state-transition microsimulation was used to estimate residual lifetime and 10-year osteoporotic fracture risks [14]. The model structure and validations have been previously documented in detail [14]. Briefly, the model simulates the most significant clinical outcomes of osteoporosis, i.e. hip, clinical vertebral and wrist fractures [15], using a patient-level microsimulation approach. Four basic disease states were constructed: “no history of fractures”, “fractured”, “post-fracture” and “death” [14]. The simulated subjects in the model are able to transit between the disease states with a 1-year cycle length until they die or until the termination of the simulation. Residual lifetime and 10 years were used for the simulation time horizons to estimate the lifetime fracture risk and 10-year first fracture risk respectively.

Tracker variables were used to record changing patient characteristics over the course of the simulation periods, like the evolving history of fracture at various sites. Transition probabilities were based on age and sex, osteoporosis prevalence, annual fracture risks and mortality rates, and were retrieved from Chinese population-specific sources whenever possible.

5.4.2 Model parameters

A summary of the main parameters included in the model is shown in *Table 5.1*. The initial distribution of the simulated patients was based on the prevalence of osteoporosis in the Chinese population [16]. We used the World Health Organization (WHO) diagnosis standard to define osteoporosis: i.e. hip (femoral neck) bone mineral density (BMD) 2.5 standard deviation (SD) or more below the young adult female mean (i.e., T-score≤-2.5) [15]. Non-osteoporotic subjects in the model could become osteoporotic during the simulation. The probability of developing osteoporosis was calculated from the difference in osteoporosis prevalence between each 10 year age band plus the mortality rate for that age band [14, 16, 17]. In summary, the calculated risks of developing osteoporosis were 0.011, 0.014, 0.018 and 0.033 person-years for women aged 50-59, 60-69, 70-79 and 80+ years respectively. Similarly, the calculated risks were 0.004, 0.0036 and 0.009 person-years for men aged 50-59, 60-69 and 70+ years respectively. We have validated our calculations by comparing the model predicted age-specific osteoporosis prevalence against that from the literature using cohort analyses [14].

Annual fracture incidence rates were obtained from recent Chinese studies wherever available [18-20]: annual hip fracture rates were obtained from a study in Hefei, a moderately developed city of 1.7 million inhabitants located in central China [20] and annual clinical vertebral fracture rates were retrieved from a study in Hong Kong (located in southern China) [19]. As there are no Chinese data, annual wrist fracture rates were taken from a Norwegian study and calibrated to Asian populations with a fracture relative risk of 0.72 (95% CI: 0.53-1.00) [18]. Fracture rates for simulated subjects with and without osteoporosis were applied based on the proportion of osteoporosis attributed fractures in those two populations according to well accepted methodology [21].

Age-specific mortality rates for the general population were taken from the China Public Health Statistical Yearbook 2012 [17]. No excess mortality was assumed for patients with osteoporosis without fractures [22], and increases in mortality were assumed for patients who sustained a fracture in the year following that fracture [22]: the standardized mortality ratios (SMRs) for men who sustain a hip, vertebral and wrist fracture were 3.51 (95% CI: 2.65-4.66), 2.12 (95%

CI: 1.66-2.72) and 1.33 (95% CI: 0.99-1.80) respectively. Similarly, the SMRs for women were 2.43 (95% CI: 2.02-2.93), 1.82 (95% CI: 1.52-2.17) and 1.42 (95% CI: 1.19-1.70) respectively.

5.4.3 Analyses

Microsimulation (or patient-level simulation), in which only one simulated subject transits through the model at one time, was used to determine the residual lifetime and 10-year fracture risks. Uncertainties, including stochastic (first-order) and parameter (second-order) uncertainties, were addressed [23]. First-order uncertainty comes from the probabilistic structure of the health economics model, and this random variation can be reduced by increasing the number of simulated subjects [24]. Second-order uncertainties relate to the uncertainties around the model input parameters and were addressed through probabilistic sensitivity analysis (PSA), or the simultaneous sampling of all relevant distributions around the input variable values [25].

A total of 100 samples × 5,000 individual simulations were performed, i.e. distributions were sampled 100 times (samples), and after each sample, 5,000 simulated subjects were run through the model using the sampled values. Mean and 95% confidence interval (CI) of the residual lifetime and 10-year fracture risks were calculated. The health economics model was constructed and all the statistical analyses were performed using TreeAge Pro Suite 2014 (TreeAge Software, Williamstown, Massachusetts).

5.5 Results

Absolute residual lifetime and 10-year risks of first osteoporotic hip, clinical vertebral, wrist or any of these fractures are shown in *Tables 5.2&3 and Figure 5.1*. Overall, residual lifetime and 10-year risks of the first osteoporotic fracture in women were higher than those projected for men at any fracture site across the ages 50 to 90 years.

At the age of 50 years, 40.9% (95% CI: 38.3-44.0%) of Chinese women were estimated to sustain a major (hip, clinical vertebral or wrist) osteoporotic fracture in the remaining life, whereas the probability in men was estimated to be 8.7% (95% CI: 7.5-9.8%). Residual lifetime risks of the first clinical vertebral fracture were higher than those of hip fracture and wrist fracture in both sexes. The pattern of residual lifetime risks with age varied for different fracture sites and by sex (*Figure 5.1*). For hip fracture, residual lifetime risks remained relatively constant until the age of 80 years in men and 75 years in women, then decreased with age. For clinical vertebral fracture, residual lifetime risks remained constant in men up to the age of 80

years whereas the residual lifetime risks decreased progressively with age in women. A similar pattern was observed for wrist fractures and any major osteoporotic fractures.

The absolute 10-year risks of the first major osteoporotic fracture were estimated to be 8.2% (95% CI: 6.8-9.3%) for women aged 50 years and 1.2% (95% CI: 0.8-1.7%) for men respectively. The pattern of 10-year fracture risks were similar in different fracture sites in women and men. Risk increased up to the age of 80 years and then declined and approached the residual lifetime fracture risks at the age of 90 years (*Figure 5.1*).

Table 5.1. Key parameters in the model

Parameter	Women	Men	Distribution
Prevalence of osteoporosis (%) [16]	3.5 (50-59 years), 14.2 (60-69 years), 26.8 (70-79 years), 39.2 (80+ years)	2.2 (50-59 years), 6.2 (60-69 years), 9.8 (70-79 years), 18.8 (80+ years)	-
Fracture incidence (annual rate per 1,000 person-years)			
Hip [20]	0.33 (50-54 years), 0.46 (55-59 years), 0.54 (60-64 years), 0.96 (65-69 years), 2.33 (70-74 years), 4.08 (75-79 years), 6.44 (80-84 years), 6.59 (85-89 years), 8.67 (90+ years)	0.44 (50-54 years), 0.48 (55-59 years), 0.46 (60-64 years), 0.65 (65-69 years), 1.26 (70-74 years), 2.37 (75-79 years), 5.19 (80-84 years), 5.71 (85-89 years), 8.35 (90+ years)	-
Clinical vertebral [19]	2.19 (50-54 years), 3.13 (55-59 years), 5.16 (60-64 years), 5.64 (65-69 years), 8.74 (70-74 years), 12.05 (75-79 years), 21.19 (80-84 years), 26.89 (85-89 years), 27.10 (90+ years)	0.50 (50-54 years), 1.11 (55-59 years), 1.65 (60-64 years), 0.95 (65-69 years), 2.26 (70-74 years), 4.50 (75-79 years), 5.94 (80-84 years), 9.54 (85-89 years), 10.85 (90+ years)	-
Wrist [18]	4.76 (50-54 years), 7.32 (55-59 years), 11.16 (60-64 years), 12.95 (65-69 years), 13.17 (70-74 years), 13.87 (75-79 years), 15.01 (80-84 years), 15.10 (85-89 years), 13.97 (90+ years)	1.37 (50-54 years), 1.22 (55-59 years), 1.42 (60-64 years), 2.35 (65-69 years), 2.01 (70-74 years), 2.25 (75-79 years), 3.42 (80-84 years), 3.44 (85-89 years), 2.33 (90+ years)	-
Mortality rate (per 1,000) for general population [17]	2.12 (50-54 years), 3.48 (55-59 years), 6.05 (60-64 years), 10.31 (65-69 years), 20.36 (70-74 years), 37.84 (75-79 years), 69.98 (80-84 years), 136.03 (85+ years)	5.14 (50-54 years), 7.87 (55-59 years), 11.66 (60-64 years), 18.53 (65-69 years), 32.12 (70-74 years), 55.18 (75-79 years), 92.94 (80-84 years), 156.07 (85+ years)	-
Relative risks of wrist fractures in Asians versus Caucasians [18]	0.72 (95% CI: 0.53-1.00)	0.72 (95% CI: 0.53-1.00)	Beta
Osteoporosis attribution probabilities for hip fractures [21]	0.75 (Range: 0.20-0.85) for 50-64 years, 0.85 (Range: 0.50-0.95) for 65-84 years, 0.95 (Range: 0.60-0.95) for 85+ years	0.55 (Range: 0.10-0.65) for 50-64 years, 0.75 (Range: 0.15-0.90) for 65-84 years, 0.85 (Range: 0.30-0.95) for 85+ years	Triangular
Osteoporosis attribution probabilities for clinical vertebral fractures [21]	0.75 (Range: 0.40-0.80) for 50-64 years, 0.85 (Range: 0.50-0.95) for 65-84 years, 0.95 (Range: 0.60-0.95) for 85+ years	0.60 (Range: 0.30-0.80) for 50-64 years, 0.75 (Range: 0.40-0.90) for 65-84 years, 0.85 (Range: 0.50-0.95) for 85+ years	Triangular
Osteoporosis attribution probabilities for wrist fractures [21]	0.60 (Range: 0.10-0.70) for 50-64 years, 0.70 (Range: 0.35-0.80) for 65-84 years, 0.70 (Range: 0.55-0.90) for 85+ years	0.30 (Range: 0.30-0.55) for 50-64 years, 0.35 (Range: 0.15-0.50) for 65-84 years, 0.40 (Range: 0.30-0.50) for 85+ years	Triangular
SMR after a hip fracture [22]	2.43 (95% CI: 2.02-2.93)	3.51 (95% CI: 2.65-4.66)	Gamma
SMR after a clinical vertebral fracture [22]	1.82 (95% CI: 1.52-2.17)	2.12 (95% CI: 1.66-2.72)	Gamma
SMR after a wrist fracture [22]	1.42 (95% CI: 1.19-1.70)	1.33 (95% CI: 0.99-1.80)	Gamma

CI=confidence interval, SMR=standardised mortality ratios.

Table 5.2. Residual lifetime risk (%) of the first osteoporotic fracture in men and women by age

Age (years)	Hip fracture		Clinical vertebral fracture		Wrist fracture		Any of these fractures	
	Men	Women	Men	Women	Men	Women	Men	Women
50	2.9 (2.5-3.3)	6.4 (5.8-7.0)	4.2 (3.7-4.6)	19.1 (18.0-20.5)	1.6 (1.3-1.9)	15.4 (14.5-16.5)	8.7 (7.5-9.8)	40.9 (38.3-44.0)
55	2.9 (2.3-3.3)	5.5 (4.8-6.1)	4.2 (3.7-4.7)	16.4 (15.4-17.5)	1.6 (1.1-1.9)	12.3 (11.3-13.2)	8.7 (7.1-9.9)	34.2 (31.5-36.8)
60	2.9 (2.6-3.5)	5.4 (4.9-6.0)	4.1 (3.5-4.8)	16.1 (15.0-17.0)	1.5 (1.1-1.8)	11.6 (10.6-12.7)	8.5 (7.2-10.1)	33.1 (30.5-35.7)
65	3.0 (2.5-3.4)	5.4 (4.8-5.9)	4.1 (3.7-4.6)	15.3 (14.5-16.2)	1.3 (0.9-1.6)	10.1 (9.3-10.9)	8.4 (7.1-9.6)	30.8 (28.6-33.0)
70	3.1 (2.6-3.7)	5.4 (4.8-5.8)	4.2 (3.7-4.8)	14.9 (14.0-15.8)	1.1 (0.8-1.4)	8.6 (7.7-9.4)	8.4 (6.9-9.8)	28.9 (26.5-31.0)
75	3.3 (2.9-3.7)	5.2 (4.6-5.8)	4.3 (3.7-4.8)	14.4 (13.6-15.3)	1.0 (0.8-1.2)	7.0 (6.4-7.8)	8.6 (7.4-9.7)	26.6 (24.6-28.9)
80	3.4 (3.0-3.9)	4.7 (4.3-5.5)	4.3 (3.6-4.8)	13.7 (12.8-14.6)	0.9 (0.6-1.1)	5.4 (4.8-6.0)	8.6 (7.2-9.8)	23.8 (21.9-26.1)
85	2.9 (2.4-3.3)	3.9 (3.2-4.4)	3.7 (3.2-4.2)	12.4 (11.7-13.3)	0.6 (0.4-0.8)	4.1 (3.5-4.7)	7.2 (6.0-8.3)	20.4 (18.4-22.4)
90	2.6 (2.2-3.1)	3.3 (2.9-3.8)	2.9 (2.3-3.3)	9.7 (9.0-10.4)	0.3 (0.2-0.5)	2.9 (2.4-3.4)	5.8 (4.7-6.9)	15.9 (14.3-17.6)

All values are presented with mean and 95% confidence interval.

Table 5.3. 10-year risk (%) of the first osteoporotic fracture in men and women by age

Age (years)	Hip fracture		Clinical vertebral fracture		Wrist fracture		Any of these fractures	
	Men	Women	Men	Women	Men	Women	Men	Women
50	0.3 (0.2-0.4)	0.6 (0.3-0.8)	0.6 (0.4-0.8)	3.4 (2.9-3.9)	0.3 (0.2-0.5)	4.2 (3.6-4.6)	1.2 (0.8-1.7)	8.2 (6.8-9.3)
55	0.3 (0.2-0.5)	0.4 (0.3-0.6)	0.8 (0.6-1.1)	3.0 (2.6-3.4)	0.5 (0.3-0.6)	3.8 (3.3-4.3)	1.6 (1.1-2.1)	7.2 (6.2-8.3)
60	0.5 (0.3-0.7)	0.7 (0.4-0.9)	0.9 (0.6-1.1)	4.1 (3.4-4.5)	0.6 (0.4-0.8)	5.0 (4.4-5.6)	2.0 (1.3-2.6)	9.8 (8.2-11.0)
65	0.8 (0.6-1.0)	1.3 (1.1-1.7)	1.4 (1.1-1.7)	5.3 (4.6-5.9)	0.6 (0.4-0.9)	5.4 (4.7-5.9)	2.8 (2.1-3.6)	12.0 (10.4-13.5)
70	1.5 (1.1-1.8)	2.4 (2.0-2.8)	2.3 (1.8-2.8)	7.3 (6.7-8.1)	0.7 (0.5-0.9)	5.5 (4.8-6.1)	4.5 (3.4-5.5)	15.2 (13.5-17.0)
75	2.3 (1.9-2.7)	3.5 (3.0-3.9)	3.1 (2.6-3.6)	10.0 (9.2-10.9)	0.8 (0.5-1.0)	5.4 (4.9-6.1)	6.2 (5.0-7.3)	18.9 (17.1-20.9)
80	2.9 (2.5-3.4)	3.9 (3.5-4.2)	3.8 (3.3-4.4)	12.0 (11.1-12.7)	0.8 (0.6-1.1)	4.7 (4.2-5.2)	7.5 (6.4-8.9)	20.6 (18.8-22.1)
85	2.7 (2.3-3.1)	3.6 (3.0-4.1)	3.6 (3.1-4.1)	11.8 (11.1-12.7)	0.6 (0.4-0.8)	3.8 (3.3-4.4)	6.9 (5.8-8.0)	19.2 (17.4-21.2)
90	2.6 (2.1-3.0)	3.2 (2.8-3.7)	2.8 (2.2-3.2)	9.5 (8.8-10.2)	0.3 (0.2-0.5)	2.8 (2.4-3.3)	5.7 (4.5-6.7)	15.5 (14.0-17.2)

All values are presented with mean and 95% confidence interval.

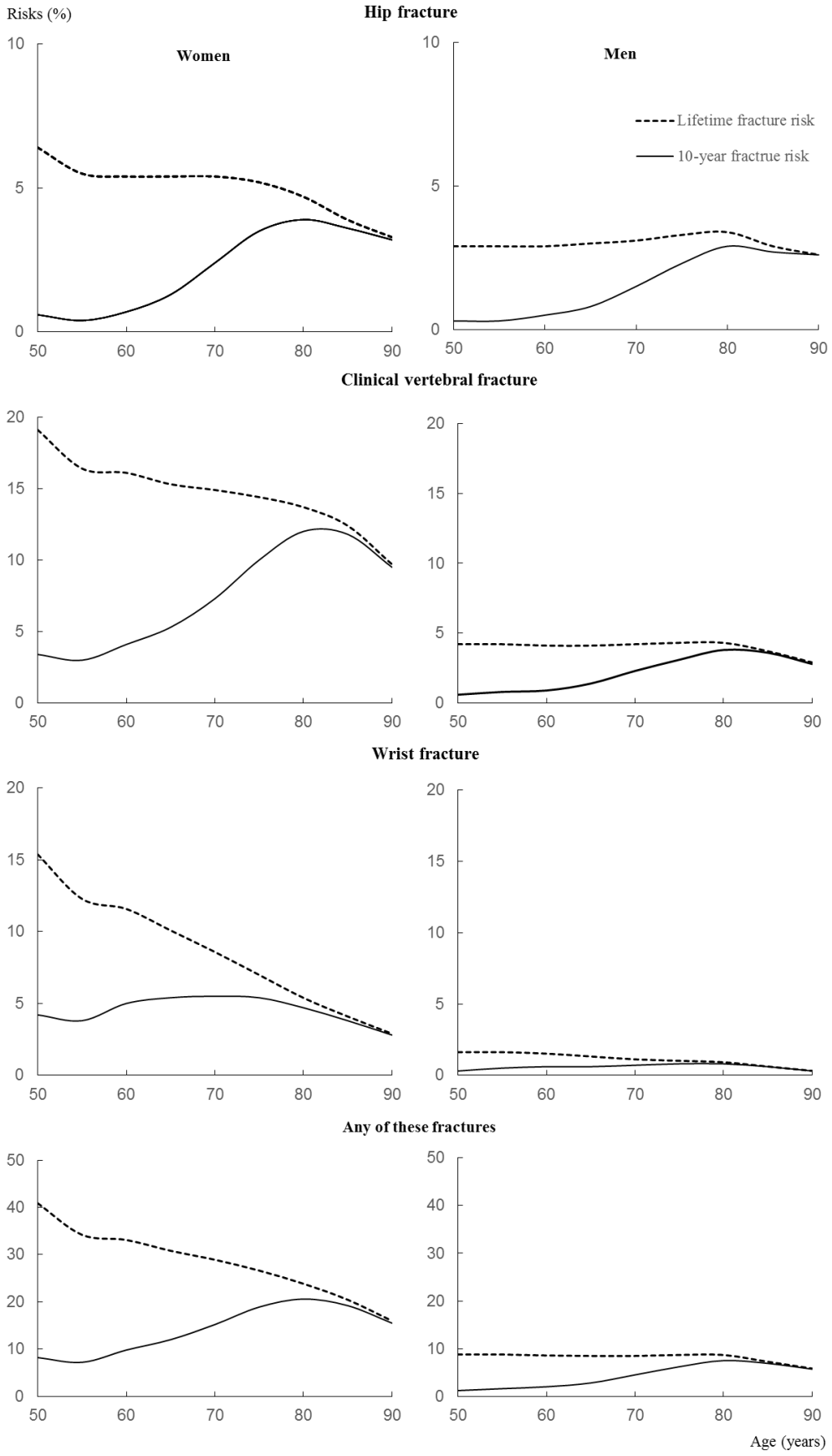

Figure 5.1. Residual lifetime and 10-year risks of the first hip, clinical vertebral, wrist or any of these osteoporotic fractures for Chinese men and women by age.

5.6 Discussion

Understanding the absolute risks of the first osteoporotic fracture is of value to estimate the future burden of osteoporosis to society. To our knowledge, this is the first study to determine the residual lifetime and 10-year absolute risks of the first hip, clinical vertebral, wrist or any major osteoporotic fracture in Chinese men and women using a health economics model. It is estimated that more than one third of Chinese women and approximately one in ten Chinese men aged 50 years are expected to sustain a major (hip, clinical vertebral or wrist) osteoporotic fracture in their remaining lifetimes. Chinese women are estimated to have much higher residual lifetime and 10-year risks of osteoporotic clinical vertebral and wrist fractures, but the difference in 10-year risks of hip fractures are relatively small between men and women (*Table 5.3 and Figure 5.1*).

The estimated risks of osteoporotic fractures in the Chinese population from our study are consistent with those in previous studies which have been found lower than those in Caucasians [7, 8, 26-29] and some other Asian populations [9, 10], but the residual lifetime hip fracture risk at age 50 years was noticeably higher than the earlier estimation for the Chinese population [11] (*Table 5.4*). The reasons for the increase are threefold: First, the incidence of hip fractures has significantly increased in the past decades; this secular trend was not only observed in China but in other areas [10, 13, 30, 31]. Second, the proportion of Chinese population aged 65 years and above has grown with the ageing population [32]. Finally, the life expectancy has also increased by approximately 3 years between 2000 and 2010 [33]. Based on the above three factors, the residual lifetime hip fracture risk, the result of competing risks between mortality and fracture, has increased from 2.4% for women and 1.9% to men in 2002 to 6.4% for women and 2.9% for men aged 50 years.

10-year absolute fracture risks increased with age until annual mortality risks out-competed the fracture risks. In our study, the turning points for the 10-year fracture risks occur at age 80 years in both sexes (*Figure 5.1*), and decrease with age thereafter. The 10-year fracture risks approach the residual lifetime fracture risks above age 90 years, as very few people are expected to live above the age of 100 years [33].

In this study, a validated state-transition microsimulation model was used to estimate the residual lifetime and 10-year absolute fracture risks. Health economics models have been extensively used in risk predictions not only in osteoporosis but in other diseases [7, 28, 34-38]. By using this approach, the simulated subjects were analysed for the residual lifetime or a

defined time period. More importantly, this health economics model can be used to identify the interventions that represent good value for money when it includes costs and effectiveness in the model analysis, i.e. cost-effectiveness analysis. Precise estimates of the residual lifetime fracture risks for scenarios with and without fracture preventions are of value to the healthcare policy maker to leverage scarce resources, therefore future studies are encouraged be performed to identify the cost-effective fracture prevention strategies given the increased residual lifetime and 10-year fracture risks in the Chinese population.

Table 5.4. Comparison of residual lifetime osteoporotic fracture risks (%) across countries at age 50 years

Country	Year of publication	Hip fracture		Vertebral fracture		Wrist fracture	
		Men	Women	Men	Women	Men	Women
China [11]	2012	1.9	2.4	-	-	-	-
Current study	-	2.9	6.4	4.2	19.1	1.6	15.4
Australia [27]	2001	2.0	7.0	6.0	8.0	5.0	12.0
Canada [8]	2012	6.2	7.3	-	-	-	-
Korea [9]	2011	5.2	12.3	-	-	4.9	21.7
Australia [28]	2001	-	17.0	-	9.6	-	-
Japan [10]	2009	5.6	20.0	-	-	-	-
Sweden [26]	2000	10.7	22.9	8.3	15.1	4.6	20.8
Belgium [7]	2008	-	24.8	-	13.9	-	18.1
Norway [29]	2009	18.3	30.4	-	-	6.2	32.7

There are potential limitations to our study. First, regional hip and clinical vertebral fracture incidence rates were used, which might not be representative of the whole country. Large variations in fracture risks within the same country were reported in previous study [27]. It would be preferable to use fracture incidences from several regions or country level data if these were available, particularly for countries like China whose population has different ethnic groups and risks factors. Second, because of the paucity of data on wrist fracture incidence in the Chinese population, wrist fracture rates from a Norwegian study were used and calibrated to the Asian population using a 0.72 fracture relative risk. Nevertheless, the generalizability of the results is a major concern, updated study using data from a country-level survey on different fracture sites is required. Third, we only included hip, clinical vertebral and wrist fractures in this study, fractures at other sites like tibia, humerus, ribs and pelvis were omitted. Therefore, our study potentially underestimated the residual and 10-year risks of all major osteoporotic fractures. Fourth, only two risk factors (sex and age) were included in this study. Other risk

factors such as smoking, high intake of alcohol and rheumatoid arthritis that might influent the fracture risks were not included [39]. In addition, we assumed that the risk of fractures will remain stable over simulation time horizon. However, because of the new medications to prevent fractures were publically available and the increasing awareness of the significance of osteoporosis, recent studies demonstrated that the fracture risks have decreased in some countries like Australia [11]. In contrast, in countries like China, Japan, Turkey, hip fracture risks kept rising in the past decade [11, 13, 30]. Finally, despite the fact that we only accounted for the first fracture in simulated subjects, patients with fracture history might also have been included in the original studies. Because fracture risks for patients with prior fractures are higher than those who do not have a history of fracture, the probability used may be higher than the probability of having a first fracture and in turn the residual lifetime and 10-year risks of having a first fracture are potentially overestimated. Due to a lack of published information on distributions around fracture incidence rates, osteoporosis prevalence and mortality rates for the general population, point estimates only were used for these parameters.

Nonetheless, the results in this study present the best estimates with currently available data. Osteoporosis has been listed as one of the National Health Priorities (NHPs) since 2011, because of its substantial disease and financial burden to the Chinese healthcare system. The costs of osteoporotic fractures were estimated to double by 2035 due to rapidly ageing Chinese population [4], health economics evaluation studies are urgent to be performed to find the fracture preventions that present good value for money. To date, several fracture prevention drugs in the National Drug List are publically funded. However, no health economics evidence was provided for most of these drugs. As a result, cheap drugs such as calcitonin is still dominantly used in China [40], while its cost-effectiveness comparing with alendronate is inconclusive due to highly sensitive efficacy of calcitonin [41]. Some other drugs, such as denosumab, were proved to be cost-effective in the Caucasian population [42], but were not reimbursed from the public health insurance. With the baseline fracture risks from the current study, future work is urgently needed to identify the cost-effective osteoporosis screening strategies and fracture prevention medications using a Chinese country-specific health economics evaluation model [14].

More than one third of Chinese women and around one tenth Chinese men aged 50 years are expected to sustain the first osteoporotic (hip, clinical vertebral or wrist) fracture in the remaining life. Risks of fractures have increased in the past decade in Chinese men and women.

While fracture risks estimates are lower in Chinese than Caucasian populations, it is clear that osteoporotic fractures will still produce a major burden for the Chinese health system and the prevention of osteoporosis is an issue which requires serious attention. Without targeted interventions, fracture risks may continue to increase in the future which in turn pose a major challenge to the healthcare system and also healthcare resources allocation.

5.7 References

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Chapter 6: Projection of osteoporosis-related fractures and costs in China: 2010-2050

6.1 Preface

This chapter presents the second application of our osteoporosis health economics model. Estimates of current and future number as well as economic burden of osteoporotic fractures to the Chinese healthcare system are provided. Around 2.33 million osteoporotic fractures occurred in 2010, costing the Chinese healthcare system approximately $9.45 billion. Annual number and costs of osteoporosis-related fractures are estimated to double by 2035 and will increase to 5.99 million fractures costing $25.43 billion by 2050. Consequently, cost-effective intervention policies must urgently be identified in an attempt to minimize the impact of fractures: a subject of Chapter 7's investigation.

This chapter has been published in *Osteoporosis International* (Appendix 6A).

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The published article of this chapter appears in an appendix to the chapter. It has been removed for copyright or proprietary reasons.

6.2 Abstract

Introduction: The aim of the study was to project the osteoporosis-related fractures and costs for the Chinese population aged ≥50 years from 2010 to 2050.

Methods: A state-transition microsimulation model was used to simulate the annual incident fractures and costs. The simulation was performed with a 1-year cycle length and from the Chinese healthcare system perspective. Incident fractures and annual costs were estimated from 100 unique patient populations for year 2010, by multiplying the age- and sex-specific annual fracture risks and costs of fracture by the corresponding population totals in each of the 100 categories. Projections for 2011-2050 were performed by multiplying the 2010 risks and costs of fracture by the respective annual population estimates. Costs were presented in 2013 US dollars.

Results: Approximately 2.33 (95% CI: 2.08, 2.58) million osteoporotic fractures were estimated to occur in 2010, costing $9.45 (95% CI: 8.78, 10.11) billion. Females sustained approximately 3 times more fractures than males, accounting for 76% of the total costs from 1.85 (95% CI: 1.68, 2.01) million fractures. Annual number and costs of osteoporosis-related fractures were estimated to double by 2035 and will increase to 5.99 (95% CI: 5.44, 6.55) million fractures costing $25.43 (95% CI: 23.92, 26.95) billion by 2050.

Conclusions: Our study demonstrated that osteoporosis-related fractures cause a substantial economic burden which will markedly increase over the coming decades. Consequently, healthcare resource planning must consider these increasing costs, and cost-effective screening and intervention policies must urgently be identified in an attempt to minimize the impact of fractures on the health of the burgeoning population as well as the healthcare budget.

6.3 Introduction

Osteoporosis and osteoporotic fractures are global concerns both affecting the quality of life and incurring a high economic burden to patients and society [1, 2]. The prevalence of osteoporosis has been estimated at approximately 13% in the Chinese population, which is lower than that seen in Caucasian populations [3]. The risk of fractures increases with age [4], so the number of osteoporotic fractures will inevitably increase due to the ageing Chinese population [5].

Worldwide, it was estimated 9 million osteoporotic fractures occurred in 2000, of which 1.6 million were hip fractures, 1.7 million were wrist fractures and 1.4 million were clinical vertebral fractures [6]. The global annual number of hip fracture is predicted to increase to 2.6 million fractures by 2025 and 4.5 million by 2050 [7]. Similar trends have been projected for China, with annual hip fracture number predicted to be 0.69 million in 2006 and to rise to 1.64 million fractures by 2020 and 5.91 million fractures by 2050 [8]. The annual costs of hip fractures in China were estimated at approximately $2.05 billion (in 2013 US dollar) in 2006, rising to $27.48 billion and $581.97 billion by 2020 and 2050 respectively. However, there are concerns about the accuracy of the Chinese estimation as figures for annual hip fracture number were higher than the total global estimation. This is probably because the estimate assumed a constant increase in osteoporosis prevalence and there was no thorough description of methodology used to project fracture number and costs of osteoporotic fractures [8].

Due to the increase of proportion of the elderly population, increasing life expectancy and the introduction of new drugs and technologies, the total health expenditure in China had risen from $180 billion (in 2013 US dollar) in 2000 to $524 billion in 2010 [9]. Although osteoporosis has been listed as one of the National Health Priorities since 2011 because of its high disease and economic burden, a more robust estimation on number and costs of osteoporotic fractures will assist health policy makers to plan healthcare resource allocation for prevention and treatment of osteoporotic fractures in the future. Our study aimed to provide an updated estimation of number and costs of all major osteoporotic fractures by age and gender for the Chinese population aged ≥50 years from 2010 through to 2050.

6.4 Methods

6.4.1 Model overview

A published, validated state-transition microsimulation model was used to estimate the number and costs of osteoporosis-related fractures for the Chinese population aged ≥50 years. The model was constructed and validated for the use of health economics evaluations in osteoporosis. We have previously described in detail the structure of the model and the model parameters [10]. Briefly, four disease states including three types of fracture (hip, wrist and vertebral fractures) were incorporated in the model: no history of fracture, fractured, post-fracture state and death (*Figure 6.1*). Simulated people were allowed to sustain multiple fractures at different sites in their residual lifetime during simulation. The number of fracture by age, sex and sites were recorded using tracker variables.

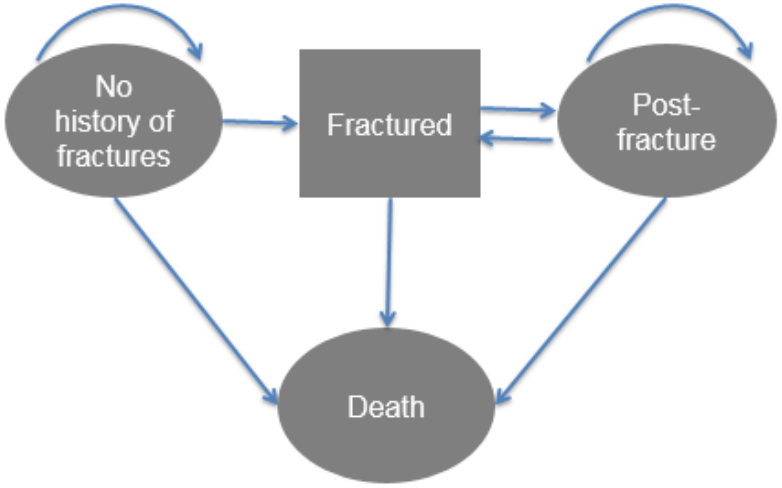

Figure 6.1. Structure of the Markov model. Simulated patients can transit between Markov states following the arrow direction, "Fractured" is a temporary state and denotes patients sustaining a hip, vertebral, wrist or other osteoporotic fracture. "Death" is an absorbing state that indicates all simulated patients will end in that state.

6.4.2 Model inputs

The key parameters in the model are summarized in *Table 6.1*. Wherever possible, published or publicly available Chinese data sources were used in our model. The transition probabilities were based on fracture and mortality rates that have been retrieved from published studies or from the China Statistical Yearbook (2013) [11-15]. Simulated subjects were assumed to have a higher mortality risk after fracture events [16, 17]. Multiple fractures at different fracture sites were accounted for in the simulation, with the risk of subsequent

fractures by site being elevated compared to that without fracture history [18, 19].

The study was performed using a healthcare system perspective, therefore direct costs (including direct medical costs and direct non-medical costs) from osteoporosis-related fractures were included. Annual costs distributions by fracture sites from a recent study in western China were used [20]. Patients were assumed to have a possibility of residing in a nursing home after hip fracture [21], and the cost of nursing home was assumed at $4,395 *per annum* [22]. All costs were converted to 2013 US dollars.

6.4.3 Annual osteoporosis-attributed fracture rates

Osteoporosis-attributed fractures refer to the fractures that would not have occurred if no osteoporosis was present according to the World Health Organization standard, i.e.: hip (femoral neck) bone mineral density (BMD) 2.5 standard deviation (SD) or more below the young adult mean (i.e. T-score $\leq$-2.5) [23]. Osteoporosis attribution probabilities by fracture site, sex and age were retrieved from the study by Melton et al. [24]. Using these probabilities and the annual fracture rates reported in the published literature (*Table 6.1*) [13-15], the annual osteoporotic fracture rates were calculated by fracture site, sex and age.

6.4.4 Model validation

By way of internal validation, goodness-of-fit analysis was performed to test whether the model could correctly reproduce the input parameters. A linear curve was fitted with the least distance between the fitted line and all of the data points [25-27], and the squared linear correlation coefficient (R^2), which was an index of the degree to which the data variation can be explained, was generated from the linear regression model. In this study, we compared the hip, clinical vertebral and wrist annual fracture rates by age and sex from model outputs against those from the reference studies.

Table 6.1. Key parameters in the model

Parameter	Women	Men	Distribution
Prevalence of osteoporosis (%) [11]	3.5 (50-59 years), 14.2 (60-69 years), 26.8 (70-79 years), 39.2 (80+ years)	2.2 (50-59 years), 6.2 (60-69 years), 9.8 (70-79 years), 18.8 (80+ years)	-
Fracture incidence (annual rate per 1,000 person-years)			
Hip [15]	0.33 (50-54 years), 0.46 (55-59 years), 0.54 (60-64 years), 0.96 (65-69 years), 2.33 (70-74 years), 4.08 (75-79 years), 6.44 (80-84 years), 6.59 (85-89 years), 8.67 (90+ years)	0.44 (50-54 years), 0.48 (55-59 years), 0.46 (60-64 years), 0.65 (65-69 years), 1.26 (70-74 years), 2.37 (75-79 years), 5.19 (80-84 years), 5.71 (85-89 years), 8.35 (90+ years)	
Clinical vertebral [13]	2.19 (50-54 years), 3.13 (55-59 years), 5.16 (60-64 years), 5.64 (65-69 years), 8.74 (70-74 years), 12.05 (75-79 years), 21.19 (80-84 years), 26.89 (85-89 years), 27.10 (90+ years)	0.50 (50-54 years), 1.11 (55-59 years), 1.65 (60-64 years), 0.95 (65-69 years), 2.26 (70-74 years), 4.50 (75-79 years), 5.94 (80-84 years), 9.54 (85-89 years), 10.85 (90+ years)	
Wrist [14]	4.76 (50-54 years), 7.32 (55-59 years), 11.16 (60-64 years), 12.95 (65-69 years), 13.17 (70-74 years), 13.87 (75-79 years), 15.01 (80-84 years), 15.10 (85-89 years), 13.97 (90+ years)	1.37 (50-54 years), 1.22 (55-59 years), 1.42 (60-64 years), 2.35 (65-69 years), 2.01 (70-74 years), 2.25 (75-79 years), 3.42 (80-84 years), 3.44 (85-89 years), 2.33 (90+ years)	
Mortality rate (per 1,000) for general population [12]	2.12 (50-54 years), 3.48 (55-59 years), 6.05 (60-64 years), 10.31 (65-69 years), 20.36 (70-74 years), 37.84 (75-79 years), 69.98 (80-84 years), 136.03 (85+ years)	5.14 (50-54 years), 7.87 (55-59 years), 11.66 (60-64 years), 18.53 (65-69 years), 32.12 (70-74 years), 55.18 (75-79 years), 92.94 (80-84 years), 156.07 (85+ years)	-
Relative risks of wrist fractures in Asians versus Caucasians [14]	0.72 (95% CI: 0.53-1.00)	0.72 (95% CI: 0.53-1.00)	Beta
Osteoporosis attribution probabilities for hip fractures [24]	0.75 (Range: 0.20-0.85) for 50-64 years, 0.85 (Range: 0.50-0.95) for 65-84 years, 0.95 (Range: 0.60-0.95) for 85+ years	0.55 (Range: 0.10-0.65) for 50-64 years, 0.75 (Range: 0.15-0.90) for 65-84 years, 0.85 (Range: 0.30-0.95) for 85+ years	Triangular
Osteoporosis attribution probabilities for clinical vertebral fractures [24]	0.75 (Range: 0.40-0.80) for 50-64 years, 0.85 (Range: 0.50-0.95) for 65-84 years, 0.95 (Range: 0.60-0.95) for 85+ years	0.60 (Range: 0.30-0.80) for 50-64 years, 0.75 (Range: 0.40-0.90) for 65-84 years, 0.85 (Range: 0.50-0.95) for 85+ years	Triangular
Osteoporosis attribution probabilities for wrist fractures [24]	0.60 (Range: 0.10-0.70) for 50-64 years, 0.70 (Range: 0.35-0.80) for 65-84 years, 0.70 (Range: 0.55-0.90) for 85+ years	0.30 (Range: 0.30-0.55) for 50-64 years, 0.35 (Range: 0.15-0.50) for 65-84 years, 0.40 (Range: 0.30-0.50) for 85+ years	Triangular
SMR after a hip fracture [17]	2.43 (95% CI: 2.02-2.93)	3.51 (95% CI: 2.65-4.66)	Gamma
SMR after a clinical vertebral fracture [17]	1.82 (95% CI: 1.52-2.17)	2.12 (95% CI: 1.66-2.72)	Gamma
SMR after a wrist fracture [17]	1.42 (95% CI: 1.19-1.70)	1.33 (95% CI: 0.99-1.80)	Gamma
Costs (2013 US dollar)			
Annual nursing home [22]	4,395 (Range: 3,767-5,023)	4,395 (Range: 3,767-5,023)	Triangular
Hip fracture, first year [20]	6,462 (Range: 3,231-9,693)	6,462 (Range: 3,231-9,693)	Triangular
Vertebral fracture, first year [20]	4,884 (Range: 2,442-7,326)	4,884 (Range: 2,442-7,326)	Triangular
Wrist fracture, first year [20]	1,980 (Range: 990-2,970)	1,980 (Range: 990-2,970)	Triangular

CI=confidence interval, SMR=standardised mortality ratios.

6.4.5 Base year and projection of fractures and annual costs

Year 2010 was selected as the base year of analysis. Age-, sex- and fracture site-specific osteoporotic fracture risks and costs for 2010 were generated from simulations with a one year time horizon [28]. A total of ten million simulations (100 sampling × 100,000 trials) were performed in each of 100 independent populations (50 age groups × 2 sexes). The total Chinese population annual fracture numbers by age and sex in 2010 were estimated by multiplying the fracture rates predicted from the model with the corresponding population numbers [29]. Total costs of fractures for the base year by age and sex were calculated by multiplying the average annual costs predicted from the model by the corresponding population totals. Projections for 2011 to 2050 were performed by multiplying base-year fracture number by their respective population estimation from the World Bank [29], assuming that these fracture rates would not change over the simulated time period.

6.4.6 Statistical analysis

The state-transition microsimulation model was constructed and analysed using TreeAge Pro Suite 2014 (TreeAge Software, Williamstown, Massachusetts), and the calculation of base-year and projected fracture number and costs were performed using Microsoft Excel (Microsoft Office Professional 2013). Incidence of fractures were reported as the number of fractures divided by the population totals aged 50+ years. Uncertainties around the annual number and costs of fractures were addressed through probabilistic sensitivity analysis by sampling from distributions around the parameters, generating mean and 95% confidence intervals (CI) for annual number and costs of fractures. Due to lack of information on distributions around vertebral and wrist fracture incidence rates and population projection estimates, point estimates only were used for these parameters.

6.5 Results

6.5.1 Model validation

A total of 54 internal validations were performed by comparing model predictions of hip, clinical vertebral and wrist fracture rates by age and sex against those data used in creating our model (*Figure 6.2*). The fracture rates generated by the model accurately match the published data that had been used in model construction: the regression line slope was 0.992 and the R^2 was 0.997.

6.5.2 Base year annual fractures and costs

Annual fracture number and annual costs for the base year by age group, sex and fracture site are given in *Table 6.2.* In 2010, the model predicted that approximately 2.33 (95% CI: 2.08, 2.58) million fractures occurred, accounted for approximately 7.15 per 1,000 people aged 50+ years, costing about $9.45 billion (95% CI: 8.78, 10.11 billion US dollars) to the Chinese healthcare system. Females were estimated to sustain approximately four times the number of fractures than males, with total annual incident fractures of 1.85 and 0.48 million respectively. Females aged 60-64 years were estimated to sustain highest wrist and total fracture events, whereas hip and clinical vertebral fracture number were highest in age group 75-79 years. The annual costs were highest in age group 75-79 years. Men aged 75-79 years had the highest total costs and predicted incident hip, clinical vertebral and total fractures. Although women sustained around four times the number of fractures, due to the differing distribution amongst the site of fractures, the total costs of osteoporotic fracture in women was approximately three times than that in men ($7.18 billion versus $2.27 billion).

6.5.3 Projection of annual fractures and related cost to 2050

Projection of fractures by sex for each fracture site are given in *Figure 6.3* and *Appendix Table 6B.1.* Fracture number and related costs at the included fracture sites were estimated to increase through to 2050 in both sexes. Relative to the base year, annual total fracture number and costs were predicted to double by year 2035 (4.83 million fractures at a cost of 19.92 billion US dollars) and were projected to rise to 5.99 (95% CI: 5.44, 6.56) million fractures, accounted for approximately 9.84 per 1,000 people aged 50+ years, costing $25.43 billion (95% CI: 23.92, 26.95 billion US dollars) by year 2050.

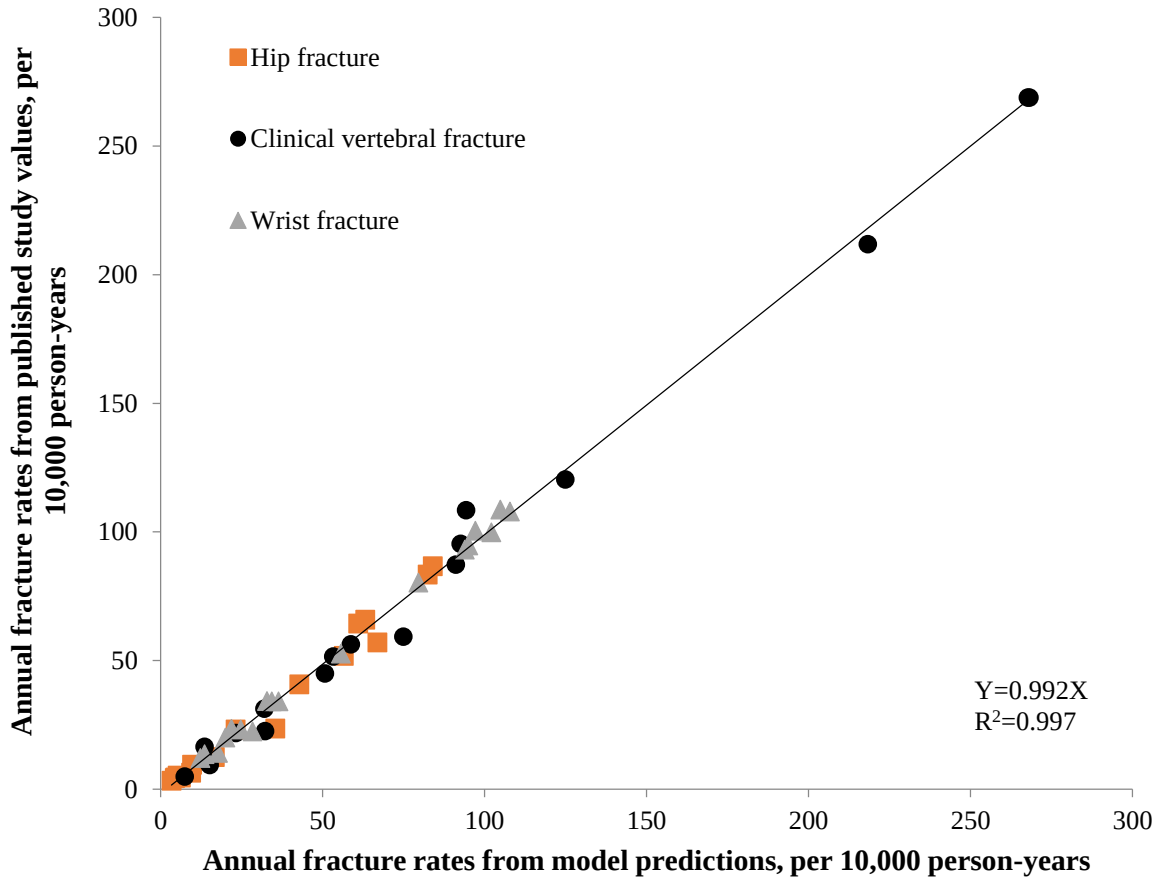

Figure 6.2. Goodness-of-fit test for model internal validation

Table 6.2. Osteoporotic incident fractures and annual costs by age group, sex and fracture site for the base-year

Stratum	Incident osteoporotic fracture number (95% CI)				Total annual costs [b] (95% CI)
	Hip	Vertebral [a]	Wrist	Total	
Female					
Age (years)					
50-54	10,713 (7,380, 14,760)	67,944 (58,653, 77,375)	86,496 (73,646, 95,865)	165,153 (139,679, 188,000)	0.57 (0.52, 0.62)
55-59	14,475 (10,351, 19,223)	101,062 (88,797, 113,779)	134,931 (120,627, 147,087)	250,469 (219,775, 280,089)	0.85 (0.78, 0.93)
60-64	14,161 (10,578, 18,158)	112,927 (101,204, 124,378)	145,263 (132,612, 158,077)	272,351 (244,394, 300,613)	0.93 (0.86, 1.00)
65-69	20,987 (17,083, 25,798)	99,431 (91,688, 107,764)	124,621 (114,349, 135,072)	245,040 (223,119, 268,634)	0.87 (0.82, 0.92)
70-74	37,281 (32,373, 42,547)	121,976 (113,480, 130,969)	104,857 (96,398, 112,538)	264,115 (242,251, 286,054)	1.04 (0.99, 1.11)
75-79	47,706 (43,340, 52,118)	132,791 (124,785, 141,015)	80,382 (75,045, 85,309)	260,879 (243,170, 278,441)	1.12 (1.07, 1.16)
80-84	40,377 (37,397, 43,606)	131,734 (125,828, 137,852)	50,954 (46,967, 54,693)	223,065 (210,193, 236,150)	1.01 (0.97, 1.04)
85-89	20,901 (19,368, 22,407)	77,641 (74,565, 80,779)	23,479 (21,901, 25,127)	122,021 (115,834, 128,313)	0.56 (0.54, 0.58)
90-94	7,613 (7,132, 8,177)	24,286 (23,314, 25,352)	6,777 (6,282, 7,253)	38,676 (36,728, 40,782)	0.18 (0.18, 0.19)
95~	1,852 (1,730, 1,970)	5,852 (5,625, 6,071)	1,615 (1,498, 1,742)	9,320 (8,853, 9,783)	0.04 (0.04, 0.05)
Sub-total	216,066 (186,733, 248,763)	875,646 (807,939, 945,334)	759,375 (689,326, 822,763)	1,851,088 (1,683,998, 2,016,860)	7.18 (6.76, 7.60)
Male					
Age (years)					
50-54	11,225 (7,094, 15,857)	19,112 (12,769, 24,119)	16,374 (12,185, 22,033)	46,711 (32,048, 62,009)	0.20 (0.15, 0.24)
55-59	12,458(8,305, 17,607)	36,633 (29,234, 43,684)	17,067 (12,042, 23,005)	66,158 (49,581, 84,296)	0.29 (0.24, 0.33)
60-64	11,452 (8,208, 15,355)	27,192 (21,999, 32,497)	16,784 (12,786, 21,329)	55,428 (42,994, 69,181)	0.24 (0.21, 0.27)
65-69	15,254 (11,647, 18,526)	21,996 (17,431, 25,991)	15,204 (11,764, 18,878)	52,455 (40,843, 63,394)	0.24 (0.20, 0.27)
70-74	22,882 (19,358, 27,016)	37,663 (33,318, 42,122)	11,717 (9,106, 14,383)	72,262 (61,781, 83,521)	0.36 (0.32, 0.39)
75-79	32,219 (29,026, 35,470)	40,210 (36,391, 44,147)	10,206 (8,187, 12,124)	82,635 (73,604, 91,740)	0.42 (0.39, 0.45)
80-84	23,569 (21,651, 25,761)	31,545 (29,358, 33,931)	6,893 (5,775, 8,087)	62,006 (56,784, 67,779)	0.32 (0.30, 0.34)
85-89	11,855 (10,837, 12,789)	15,491 (14,440, 16,586)	2,276 (1,876, 2,659)	29,622 (27,153, 32,035)	0.16 (0.15, 0.17)
90-94	3,252 (3,032, 3,514)	3,737 (3,412, 3,988)	435 (358, 518)	7,423 (6,802, 8,020)	0.04 (0.04, 0.04)
95~	720 (670, 780)	829 (753, 883)	96 (81, 114)	1,646 (1,504, 1,777)	0.01 (0.01, 0.01)
Sub-total	144,886 (119,829, 172,675)	234,408 (199,105, 267,948)	97,053 (74,160, 123,129)	476,347 (393,093, 563,753)	2.27 (0.02, 2.51)
Overall total	360,952 (306,561, 421,439)	1,110,055 (1,007,044, 1,213,282)	856,428 (763,486, 945,893)	2,327,435 (2,077,091, 2,580,613)	9.45 (8.78, 10.11)

[a] Clinical vertebral fractures. [b] Costs are presented in 2013 billion US dollars, CI = confidence interval

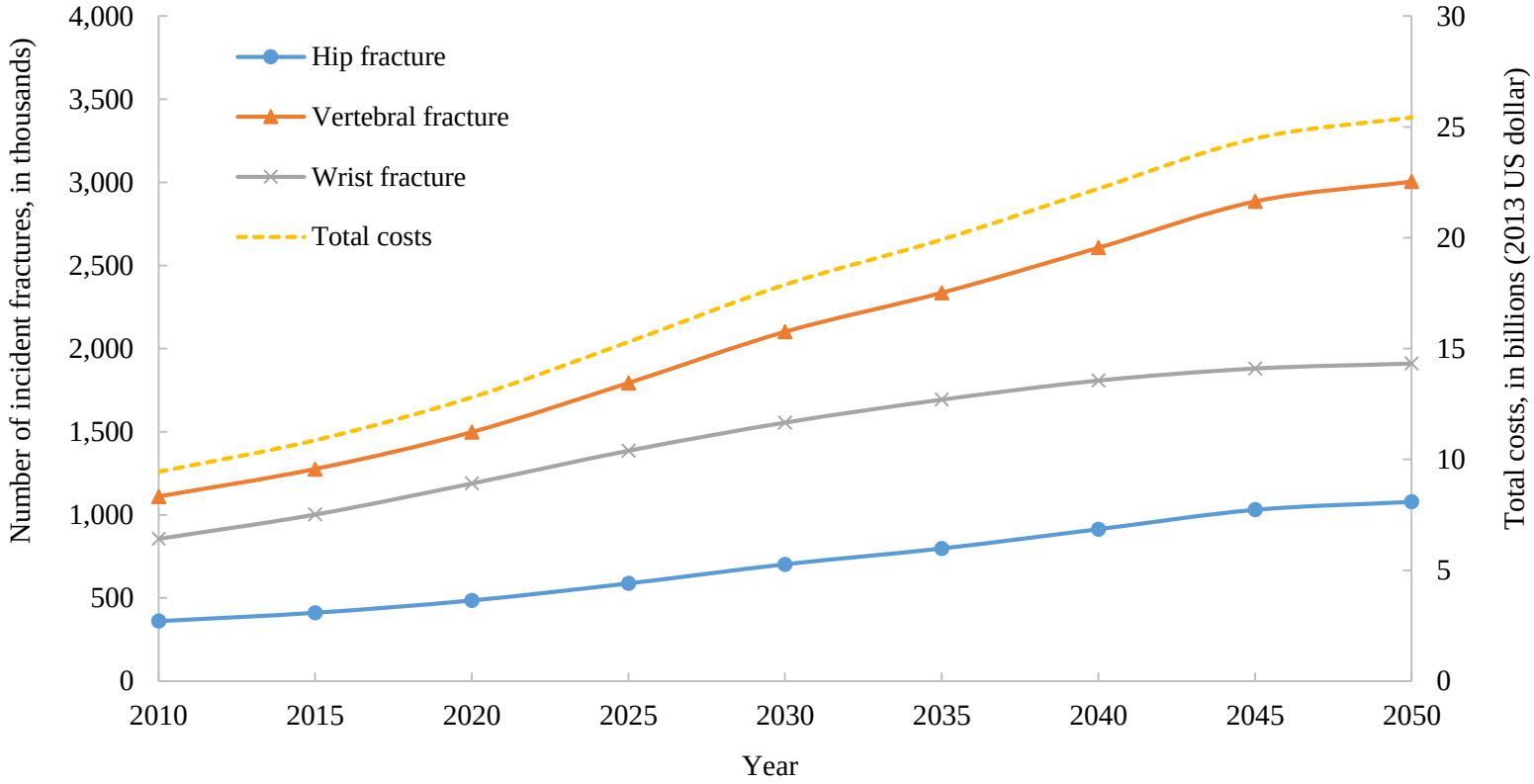

Figure 6.3. Estimation of incident osteoporosis-related fractures, i.e., fracture events that would have been avoided if osteoporosis was not presented, and costs from 2010 to 2050. Annual fracture costs for year 2010 were predicted to be $9.45 billion to the Chinese healthcare system, it is estimated to double by year 2035 ($19.92 billion) and will rise to approximately $25.43 billion by year 2050. All costs are expressed in 2013 US Dollars.

6.6 Discussion

This is the first study using a decision analytic model to estimate the osteoporosis-related fracture number and costs for the Chinese population aged ≥50 years from 2010 to 2050. To our knowledge, most previous estimates were based on the report "White Paper China 2008, Osteoporosis a Summary Statement of China" [8]. In that report, a total of 687,000 hip fractures were estimated to occur in China in 2006, with 241,000 in men and 446,000 in women over age 50-years. The number of annual hip fractures was projected to rise to 1.64 million by 2020 and 5.91 million by 2050. However, the estimations were based on the overall hip fracture incidence rate for the population aged above 50 years and assumed a steady increase of osteoporosis prevalence over the projection period. Vertebral fracture number was estimated at 1.08 million *per annum*, but only vague methodological details on how they projected fracture number were described [8]. Our study provided more robust and reproducible insight into fracture numbers by age, sex and fracture sites and annual costs over an extended time period for the Chinese population compared to previous estimations [8, 30].

For the base-year 2010, the total fracture number was estimated to be more than 2.3 million at a cost of approximately ten billion US dollars to the Chinese healthcare system. The proportion of fracture costs relative to the total health expenditure in 2010 was around 1.8% ($9.45 billion versus $524 billion) in China, which was much higher than that in the U.S. Although the total absolute costs of osteoporotic fractures were estimated at $18.7 billion in the U.S., which only took around 0.7% of its total health expenditure [28]. Approximately half of the osteoporotic fractures were clinical vertebral fractures, whereas hip and wrist fractures (0.36 million and 0.86 million respectively) accounted for the remaining 52% fractures. Notably, men contributed approximately 20% of total fracture events, which indicated osteoporotic fractures are an important public health issue for men as well as women. In particular, the difference in annual hip fracture number (0.07 million) between men and women was relatively small compared with that of total fractures (1.37 million). This is consistent with the published literature as much lower female to male ratio of hip fractures have been reported in the Chinese population [15, 31, 32] than in Caucasians [33, 34]. Different rates of hip fracture between men and women also explains the fact that although the number of all osteoporotic fractures in women is more than 4 times greater than that seen in men, the difference in costs between men and women is much smaller, as the direct costs of hip fracture are greater than those for vertebral and wrist fractures [20].

Over the 40-year projection period, the estimated number of osteoporosis-related fractures and annual costs will increase by approximately 158% and 169% respectively compared to 2010. The reasons for the increase are two-fold: first, osteoporotic fracture risks increase with age, especially after age 50 years when skeletal mass and density reductions are expected [4]. With an aging Chinese population, the proportion of population aged ≥50 is estimated to double from 24% in 2010 to 48% by 2050 [29]. Second, the population aged 75-79 years in 2050, where the highest costs were estimated to occur (*Table 6.2*), almost quadruples comparing with year 2010 (increasing by 3.01 times in men and 2.95 times in women).

State-transition models have been used in the prediction and projection of disease incidences and related costs not only in the context of osteoporosis [28, 35-37], but other diseases [38-40] in the past decades. Using a state-transition model, a variety of epidemiological sources affecting osteoporotic fracture risks, such as osteoporosis attribution probabilities for hip, vertebral or wrist fractures, are synthesised and analysed simultaneously [28, 36]. More importantly, it is possible to record the characteristics of simulated patients to more accurately predict long-term observations such as lifetime fracture risks.

Our study has some limitations. First, the projection results after 2010 were based on sex- and age-specific population estimates [29]. Therefore, the accuracy of our estimation is highly reliant on the precision of the population projection from the World Bank. Second, our study assumed that medical practice and prices in 2010 remained constant over time. In the past, new medications became available to prevent fractures [2, 30] and they had impacts on the economic burden to the healthcare system. To simplify our projections and in the absence of data on which to base assumptions about future medication effectiveness, use and costs, incorporation of assumptions about the future interventions to prevent fractures has been avoided, and we assumed that the fracture incidence rates will remain constant until 2050. Third, the age- and sex-specific incidence rates in our study were retrieved from multiple sources in different populations. Hip fracture rates were used from a recent observational study from Hefei which is located in the centre of China [15], and it is higher than previous reported incidence rates from north-east China ten years ago [31, 41] but similar to another study performed in Tangshan [5]. The clinical vertebral fracture rates were retrieved from a Southern Chinese population. Due to the lack of Chinese data, the age and gender-specific wrist fracture incidence rates were taken from a Caucasian population and calibrated to an Asian population [14, 24]. Optimally, better estimations could be achieved based on fracture incidence rates derived entirely from Chinese populations when they become available in the

future. In addition, the costs of hip, vertebral or wrist fractures were retrieved from the study in western China. Due to the differences in healthcare delivery system, demographic and socioeconomic variations, the costs of fractures might differ in other regions. Similar to the fracture number predictions, projection of fracture costs should be updated using country-level data in the future. Finally, despite hip, vertebrae and wrist being acknowledged as classic osteoporotic fracture sites, it is still hard to define what constitutes an osteoporotic fracture [42]. Recent studies have suggested "other" fracture sites like humerus, rib, pelvis, tibia and fibular fractures are also common osteoporotic fractures, and the costs and number of these "other" fractures were estimated to contribute to a high proportion of total fracture costs and incident numbers [28, 43]. However, we excluded "other" fractures in our analyses because good estimates of age-specific incidence rates, costs, standardized mortality ratios and relative risks of subsequent fractures following a fracture in "other" sites in the Chinese population have not yet been reported. Nevertheless, our study potentially underestimates the total number and economic impact of osteoporotic fractures.

Our study demonstrated that osteoporosis-related fractures cause a substantial economic burden to the Chinese healthcare system which will markedly increase over the coming decades unless action is taken. In 2010, it was estimated over 2.3 million osteoporotic fractures led to costs of approximately ten billion US dollars to the Chinese healthcare system. Number and costs of osteoporosis-related fracture are predicted to double by year 2035 and will grow to about 6 million fractures costing $25.4 billion annually by year 2050. Consequently, healthcare resource planning must consider these increasing costs, and cost-effective screening and intervention policies must urgently be identified and implemented in an attempt to minimize the impact of fractures on the health of the burgeoning population as well as the health care budget.

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Appendix Table 6B.1 Average annual incident fractures by sex and fracture sites: 2015-2050

	2015	2020	2025	2030	2035	2040	2045	2050
Female								
Hip fracture incidences	245,399	289,892	352,822	422,508	482,220	555,421	626,855	656,745
Vertebral fracture incidences [a]	1,008,193	1,184,410	1,416,285	1,662,843	1,854,752	2,067,428	2,284,375	2,384,460
Wrist fracture incidences	889,607	1,055,318	1,232,448	1,385,617	1,509,136	1,610,579	1,673,619	1,698,182
All fracture incidences	2,143,199	2,529,620	3,001,555	3,470,968	3,846,107	4,233,428	4,584,849	4,739,387
Total costs [b]	8.27	9.75	11.64	13.59	15.16	16.87	18.52	19.25
Male								
Hip fracture incidences	165,968	195,752	235,495	280,778	316,203	358,939	286,283	422,255
Vertebral fracture incidences [a]	267,593	313,268	377,356	438,733	481,315	539,336	524,568	620,885
Wrist fracture incidences	112,969	133,936	153,611	169,857	183,942	197,253	199,583	211,950
All fracture incidences	546,529	642,956	766,462	889,367	981,460	1,095,529	1,010,434	1,255,090
Total costs [b]	2.60	3.06	3.67	4.29	4.76	5.34	5.96	6.18
Total								
Hip fracture incidences	411,367	485,644	588,317	703,286	798,423	914,360	913,138	1,079,000
Vertebral fracture incidences [a]	1,275,786	1,497,678	1,793,641	2,101,576	2,336,067	2,606,764	2,808,943	3,005,345
Wrist fracture incidences	1,002,576	1,189,254	1,386,059	1,555,474	1,693,078	1,807,832	1,873,202	1,910,132
All fracture incidences	2,689,728	3,172,576	3,768,017	4,360,335	4,827,567	5,328,957	5,595,283	5,994,477
Total costs [b]	10.87	12.81	15.31	17.88	19.92	22.21	24.48	25.43

[a] Clinical vertebral fractures. [b] Costs are presented in 2013 billion US dollars

Chapter 7: Screening for osteoporosis in Chinese post-menopausal women: a health economic modelling study

7.1 Preface

This chapter presents the third application of the osteoporosis health economics model. Screening for- and appropriate treatment of osteoporosis has been proven to be cost-effective in many populations, however, it was not clear in the Chinese population. This study has demonstrated that screening for osteoporosis in Chinese women, followed by appropriate treatment is cost-effective and may even be cost-saving in Chinese post-menopausal women.

This chapter has been published in *Osteoporosis International* (Appendix 7A).

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The published article of this chapter appears in an appendix to the chapter. It has been removed for copyright or proprietary reasons.

7.2 Abstract

Introduction: This study aimed at determining the cost-effectiveness of osteoporosis screening strategies in post-menopausal Chinese women.

Methods: A validated state-transition microsimulation model with a lifetime horizon was used to evaluate the cost-effectiveness of different screening strategies with treatment of alendronate compared with current osteoporosis management in China. Osteoporosis screening strategies assessed were: 1) universal screening with dual-energy X-ray absorptiometry (DXA) alone; 2) Osteoporosis Self-Assessment Tool for Asians (OSTA) + DXA; and 3) quantitative ultrasound (QUS) + DXA with rescreening at 2, 5 or 10-year intervals for patients screening negative by DXA. The study was performed from the Chinese healthcare payer's perspective. All model inputs were retrieved from publically available literature. Uncertainties were addressed by one-way and probabilistic sensitivity analysis.

Results: Screening strategies all improved clinical outcomes at increased costs, and each were cost-effective compared with no-screening in women aged 55 years given the Chinese willingness-to-pay threshold of USD 20,000 per QALY gained. Pre-screening with QUS and subsequent DXA screening if the QUS T-score≤-0.5 with a 2-year rescreening interval was the most cost-effective strategy with the highest probability of being cost-effective across all non-dominated strategies. Screening strategies were cost-saving if screenings were initiated from age 65-year. One-way sensitivity analyses indicated the results were robust.

Conclusions: Pre-screening with QUS with subsequent DXA screening if the QUS T-score≤-0.5 with a 2-year rescreening interval in the Chinese women starting at age 55 is the most cost-effective. In addition, screening and treatment strategies are cost saving if the screening initiation age is greater than 65-year.

7.3 Introduction

Osteoporosis and osteoporosis-related fracture prevalence increase with age, especially for women after menopause [1]. Hip, vertebral and wrist fractures are regarded as major osteoporotic fractures, reflecting their relationship with increased mortality, chronic pain, disability and diminished quality of life of patients [2-4]. It is estimated that more than 40% of the Chinese women aged 50 years will have an osteoporotic fracture in their remaining lifetimes [5]. With osteoporosis prevalence among Chinese women aged 50 years and older estimated to exceed 40%, 89.2 million women will suffer from osteoporosis in 2025 [1]. Evidence has shown that more than 2 million osteoporotic fractures occurred in 2010 for the population aged over 50 years at a cost of approximately 9.5 billion US dollars (USD) to the Chinese healthcare system [6]. Moreover, the number of fractures and the costs are predicted to double by 2035 and will continue to grow in the next decades [6].

Despite the fact that osteoporosis has a substantial and increasing financial burden to the Chinese healthcare system in the coming decades, bone densitometry and a range of osteoporosis drugs are at best partly reimbursed in China [7]. In addition, people have very limited access to dual-energy X-ray absorptiometry (DXA) machines particularly in rural China. This nascent reimbursement policy and limited access to diagnostic methodologies contribute to many osteoporosis patients being undiagnosed [8].

There are numerous health economics studies on osteoporosis screening [9], many of which showed that screening for osteoporosis was cost-effective, especially in Caucasian populations [10-12]. Osteoporosis screening was, however, found to be not cost-effective in a Thai setting [13].Due to socioeconomic and population diversity, screening strategies must be performed in country- and ethnicity-specific analyses [14]. At present, there are no economic assessments supporting osteoporosis screening and treatment in China [15]. The objective of this study was to analyse the cost-effectiveness of different osteoporosis screening strategies followed by alendronate of osteoporosis detected among Chinese post-menopausal women.

7.4 Methods

7.4.1 Model description

A validated individual-level state-transition osteoporosis screening and treatment cost-effectiveness model was used. The model has been documented and validated in detail

elsewhere [16]. A brief description of the model is provided here. The model comprised four disease states: "no history of fractures", "fractured", "post-fracture" and "death", with potential fractures comprising hip, clinical vertebral and wrist fractures (*Figure 7.1*) [16]. Tracker variables were used to record characteristics of simulated subjects such as "whether fractured", "type of fractures", "time after last screening" and "time after treatment if fractured". The built-in tracker variables enabled the monitoring of patient history during the simulation, and accounted for heterogeneity of the simulated subjects.

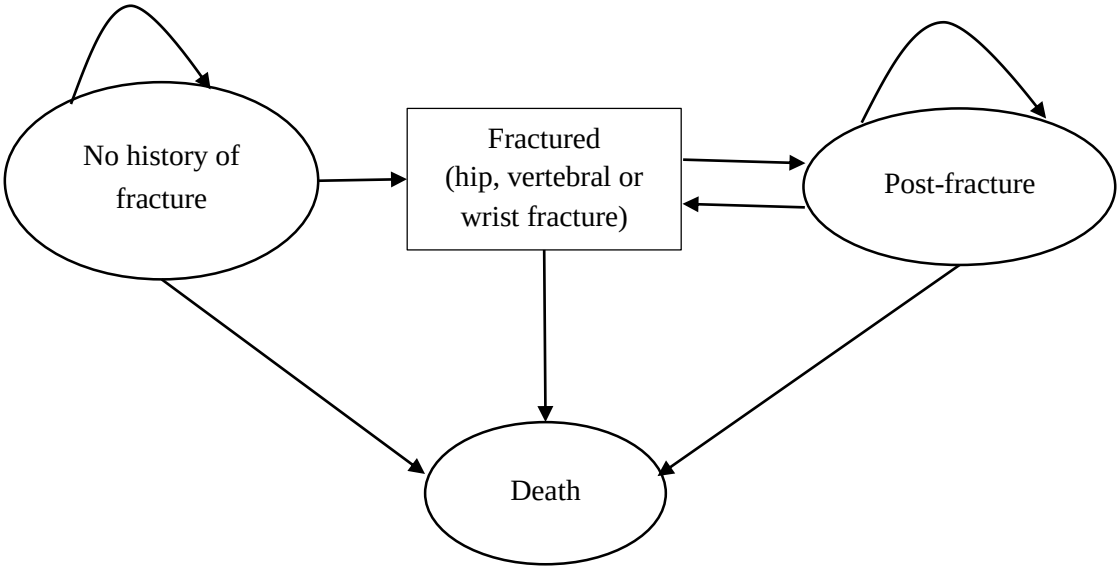

Figure 7.1. Structure of the osteoporosis state-transition model. Figure adapted from Si and colleagues [16], permission acquired from Springer. Simulated patients can transit between disease states in the direction shown by the arrow. "Fractured" is a temporary state and denotes patients with an existing osteoporotic hip, vertebral, or wrist fracture. All patients were simulated until "Death".

The World Health Organization (WHO) standard was used to define osteoporosis: i.e. hip (femoral neck) bone mineral density (BMD) 2.5 standard deviations (SDs) or more below the young adult female mean (i.e., T-score≤-2.5) [3]. Three screening techniques with a combination of 12 individual screening strategies were included as the interventions, where "no screening" was set as the comparator.

Screening strategies in this study were chosen based on the recommendations from Guidelines for the Prevention and Treatment of Primary Osteoporosis [15]. DXA scan is the

current gold standard for diagnosing osteoporosis and was therefore incorporated solely or as a confirmation test after a pre-screening strategy in the screening arms [3]. Pre-screening strategies considered were quantitative ultrasound (QUS) and Osteoporosis Self-Assessment Tool for Asians (OSTA), followed by a DXA scan for those who tested positive through either strategy.

Because osteoporosis still remains underdiagnosed in China, patients are often unaware of the disease until they have an osteoporotic fracture [17]. As a consequence, osteoporotic patients in the "no screening" arm were assumed to receive no pharmaceutical intervention unless they had an osteoporotic fracture. The type of medication they were assumed to receive reflected the current treatment pattern for osteoporotic fractures in China [18]. Currently 51% of fractured osteoporotic patients in China are reported as using calcitonin, 29% bisphosphonates [19], and the rest of the patients were assumed to receive only calcium and vitamin D supplements.

Alendronate has been selected as the treatment option in the screening arm as it is the first line treatment for osteoporosis in China [7]. Patients who tested positive through DXA across the 12 screening alternatives were assumed to receive alendronate combined with calcium and vitamin D from the time of screening for a period of five years. Otherwise, individuals were assigned to rescreening at 2, 5 or 10-year intervals. In addition, patients that were not treated after the last screening but had an osteoporotic fracture were assumed to receive alendronate following the same treatment approach in the screening arm.

We simulated female subjects with a baseline age of 55 years without a history osteoporotic hip, vertebral or wrist fractures. The population was assumed to have a mix of both osteoporotic and non-osteoporotic subjects – see section following for estimation of prevalence. The population in the model was simulated for a lifetime horizon with a one-year cycle length. The health economics evaluation was conducted from the Chinese healthcare payer's perspective. All costs were converted from Chinese Yuan to 2015 USD using International Monetary Fund purchasing power parity (PPP) values. Costs and effectiveness were discounted at 5% annually for the base-case analysis.

7.4.2 Model parameters

Wherever possible, model input values were retrieved from publically available Chinese data. The selection of model input values was based on recommendations from China Guidelines

for Pharmacoeconomic Evaluations, where results from meta-analysis based on large RCTs were the highest level, expert opinions and descriptive researches were the lowest level [18]. The major parameters included are detailed elsewhere [16], with a summary of model inputs given in *Table 7.1*.

Osteoporosis prevalence rates for the Chinese population were obtained from a recent meta-analysis and used to determine the initial probability of the simulated subjects being osteoporotic [20]. Sensitivities and specificities for pre-screenings (OSTA and QUS) in the Chinese population were determined by different T-score cut-off points [21, 22]. Age-specific mortality rates for the Chinese women were obtained from the China Public Health Statistical Yearbook 2012 [23]. Annual hip and clinical vertebral fracture rates were retrieved from epidemiological studies in the Chinese population [24, 25]. Annual wrist fracture rates were not available in the Chinese population and data from an Asian population in a Norwegian study were used [26]. Annual fracture risks that were attributed to osteoporosis were adjusted based on Melton's osteoporosis attribution rates [27], using the following formula:

$$\text{Fracture risks (osteoporosis attributed)} = \text{Annual fracture rates} \times \text{AR/P}$$

Where AR is the Melton's osteoporosis attribution rates and P denotes osteoporosis prevalence rates.

Poor adherence and persistence with osteoporosis medications is a common problem, affecting the efficacy and cost-effectiveness of osteoporosis interventions [28-33]. Both reduced adherence and persistence to medications were factored into both no screening and screening arms [34-36]. Residual fracture reduction benefits were assumed to decline over 5 years in a linear manner for those who discontinued medication [12]. Medication persistence was built in the model dependent on time after treatment. For those who were on treatment, only a proportion of them had high adherence based on medication possession ratios [34, 36].

Only direct costs were included in the analyses given a healthcare payer's perspective. Medical costs of the first year following fracture were based on a recent study in western China [19]. Annual costs for medication, nursing home residence and costs for screenings were retrieved from government recommended prices [37]. Medication costs were assumed to be zero for those who discontinued medication and 80% of annual costs for poorly adherent patients [29, 38]. Age-specific health state utility values (HSUVs) for the non-fractured population were obtained from the Chinese National Health Services Survey 2008 [4, 39]. HSUVs for individuals with a fracture were dependent on the fracture site and time

since fracture [4, 16].

7.4.3 Analyses and presentation of results

Monte Carlo probabilistic sensitivity analyses (PSA) was combined with individual-level (first-order) simulations to address stochastic and parameter uncertainties in the base-case analyses [40]. To ensure the number of simulations was sufficient, we have varied the number of samples and trials from 500 to 10,000 until the incremental costs, effectiveness and incremental cost-effectiveness ratio (ICER) became stable. Two nested simulation loops were run in our base case analyses, where the inner loop evaluated the outcomes across 1,000 trials for the given parameter values, and the 1,000 outer loop sampled those values to reflect parameter uncertainties. Mean costs and effectiveness for each strategy were aggregated, and an ICER for each screening strategy compared with no screening calculated. We used the willingness-to-pay (WTP) threshold of USD 20,000 per quality-adjusted life year (QALY) gained, approximately three times per capita Gross Domestic Product (GDP) in China, to determine whether a screening strategy was cost-effective [18]. Cost-effectiveness acceptability curves (CEACs) were generated to evaluate the probability of the osteoporosis screening strategies being cost-effective given a range of possible WTP thresholds, including one time per capita GDP [41]. One-way sensitivity analyses were performed to evaluate the robustness of ICER with changes in single parameter values in the model.

Two approaches were used to present the cost-effectiveness of the osteoporosis screening strategies. First, each individual screening strategy was compared with no screening; this approach assessed whether a screening strategy was cost-effective given the WTP threshold. Second, screening strategies were compared against each other to select the most cost-effective strategy under the WTP threshold [42]. This process included the initial exclusion of dominated strategies (a strategy with higher costs but lower effectiveness than the alternate being considered) and strategies subject to extended dominance (a strategy that with a higher ICER than the next more effective strategy).

All analyses were performed using TreeAge Pro Suite 2014 (TreeAge Software, Williamstown, Massachusetts). The presentation of the model and study results follow the CHEERS guidelines [43].

Table 7.1. Key parameters in the model

Parameter	Value	Distribution	Reference
Prevalence of osteoporosis (%)	3.5 (50-59 years), 14.2 (60-69 years), 26.8 (70-79 years), 39.2 (80+ years)	-	[20]
Fracture incidence (annual rate per 1,000 person-years)			
Hip	0.33 (50-54 years), 0.46 (55-59 years), 0.54 (60-64 years), 0.96 (65-69 years), 2.33 (70-74 years), 4.08 (75-79 years), 6.44 (80-84 years), 6.59 (85-89 years), 8.67 (90+ years)	-	[24]
Clinical vertebral	2.19 (50-54 years), 3.13 (55-59 years), 5.16 (60-64 years), 5.64 (65-69 years), 8.74 (70-74 years), 12.05 (75-79 years), 21.19 (80-84 years), 26.89 (85-89 years), 27.10 (90+ years)	-	[25]
Wrist	4.76 (50-54 years), 7.32 (55-59 years), 11.16 (60-64 years), 12.95 (65-69 years), 13.17 (70-74 years), 13.87 (75-79 years), 15.01 (80-84 years), 15.10 (85-89 years), 13.97 (90+ years)	-	[26]
Mortality rate (per 1,000) for general population	2.12 (50-54 years), 3.48 (55-59 years), 6.05 (60-64 years), 10.31 (65-69 years), 20.36 (70-74 years), 37.84 (75-79 years), 69.98 (80-84 years), 136.03 (85+ years)	-	[23]
RRs of wrist fractures in Asians versus Caucasians	0.72 (95% CI: 0.53-1.00)	Lognormal	[26]
Osteoporosis attribution probabilities for hip fractures	0.75 (Range: 0.20-0.85) for 50-64 years, 0.85 (Range: 0.50-0.95) for 65-84 years, 0.95 (Range: 0.60-0.95) for 85+ years	Lognormal	[27]
Osteoporosis attribution probabilities for clinical vertebral fractures	0.75 (Range: 0.40-0.80) for 50-64 years, 0.85 (Range: 0.50-0.95) for 65-84 years, 0.95 (Range: 0.60-0.95) for 85+ years	Lognormal	[27]
Osteoporosis attribution probabilities for wrist fractures	0.60 (Range: 0.10-0.70) for 50-64 years, 0.70 (Range: 0.35-0.80) for 65-84 years, 0.70 (Range: 0.55-0.90) for 85+ years	Lognormal	[27]
SMR after a hip fracture	2.43 (95% CI: 2.02-2.93)	Lognormal	[2]
SMR after a clinical vertebral fracture	1.82 (95% CI: 1.52-2.17)	Lognormal	[2]
SMR after a wrist fracture	1.42 (95% CI: 1.19-1.70)	Lognormal	[2]
RR of osteoporotic fractures with treatment			
Alendronate	Hip fracture (without prior fractures): 0.44 (0.31-0.57), Hip fracture (with prior fractures): 0.49 (0.34-0.64), Vertebral fracture (without prior fractures): 0.50 (0.35-0.65), Vertebral fracture (with prior fractures): 0.53 (0.37-0.69), Wrist fracture (without prior fractures): 0.88 (0.62-1.00), Wrist fracture (with prior fractures): 0.52 (0.36-0.68)	Lognormal	[30,31]
Calcitonin	Vertebral fracture: 0.46 (0.25-0.87), Non-vertebral fracture: 0.52 (0.22-1.23)	Lognormal	[32]
Calcium + vitamin D	0.88 (0.78-0.99)	Lognormal	[33]
Medication persistence			
Alendronate	First year: 0.571 (0.29-0.86)	-	[34]
Calcitonin	First year: 0.329 (0.16-0.49)	-	[34]
Calcium + vitamin D	First year: 0.367 (0.18-0.55)	-	[35]
Treatment duration, years	5 (2-10)	-	[12]
Probability of being high adherent to treatment			
Alendronate	First year: 0.619 (0.31-0.93)	-	[34]
Calcitonin	First year: 0.364 (0.18-0.55)	-	[34]
Calcium + vitamin D	First year: 0.600 (0.30-0.90)	-	[36]

Parameter	Value	Distribution	Reference
Screening sensitivity			
DXA at the femoral neck	1	-	[3]
OSTA (T-score cutoff threshold of -1)	0.76	-	[21]
QUS (T-score cutoff threshold of -1)	0.79	-	[22]
QUS (T-score cutoff threshold of -0.5)	0.88	-	[22]
Screening specificity			
DXA at the femoral neck	1	-	[3]
OSTA (T-score cutoff threshold of -1)	0.66	-	[21]
QUS (T-score cutoff threshold of -1)	0.58	-	[22]
QUS (T-score cutoff threshold of -0.5)	0.39	-	[22]
Average costs (2015 US dollar)			
Annual nursing home	4,395	-	[37]
Hip fracture, first year [a]	6,462	-	[19]
Vertebral fracture, first year [a]	4,884	-	[19]
Wrist fracture, first year [a]	1,980	-	[19]
Annual medication costs			
Alendronate	1,100	-	[37]
Calcitonin	717	-	[37]
Calcium + vitamin D	90	-	[37]
DXA scan	69.53	-	[37]
OSTA assessment	9.3	-	[37]
QUS scan	1.85	-	[37]
HSUVs			
Healthy/Osteoporotic population without fractures	0.772 (55-59 years), 0.728 (60-64 years), 0.702 (65-69 years), 0.685 (70-74 years), 0.669 (75-79 years), 0.655 (80-84 years), 0.643 (85+ years)	-	[39]
Hip fracture, first year [b]	0.776 (0.720-0.844)	Normal	[4]
Hip fracture, subsequent years [b]	0.855 (0.800-0.909)	Normal	[4]
Vertebral fracture, first year [b]	0.724 (0.667-0.779)	Normal	[4]
Vertebral fracture, subsequent years [b]	0.868 (0.827-0.922)	Normal	[4]
Wrist fracture, first year [b]	1.000 (0.960-1.000)	Normal	[4]
Wrist fracture, subsequent years [b]	1.000 (0.930-1.000)	Normal	[4]
Nursing home dwelling	0.400	-	[4]
Annual discount rate			
Costs	0.05	-	[18]
Effectiveness	0.05	-	[18]

CI=confidence interval, SMR=standardised mortality ratios, RR=relative risk, DXA=dual-energy X-ray absorptiometry, QUS=quantitative ultrasound, OSTA=Osteoporosis Self-Assessment Tool for Asians, HSUV=health-state utility value

[a] Direct costs include costs of outpatient consultations, inpatient care, investigations, medication, rehabilitation after fracture events, physical therapy, transportation, homecare, preventive care foods and specific equipment.

[b] Multipliers for the proportionate effects of fractures on HSUVs, calculated from Si. et al [4].

7.5 Results

7.5.1 Cost-effectiveness of osteoporosis screening strategies compared with no screening

For the base-case analysis, all screening strategies improved clinical outcomes and increased costs, but were cost-effective compared with no screening under the WTP threshold of USD 20,000/QALY gained (*Table 7.2*). The mean (SD) lifetime QALY for no screening was 11.024 (0.074) with mean (SD) lifetime costs of USD 1,440 (USD 98) per person.

7.5.2 Determination of most cost-effective strategies overall and by age group

Four strategies were included in the determination of the most cost-effective strategies after excluding the dominated and extended dominated strategies (*Table 7.3*). In general, screening strategies with shorter re-screening periods were more expensive but more effective. Strategies that only incorporated DXA, rather than combined QUS pre-screening, were more costly but more effective, although the differences in QALYs between screening strategies were relatively small.

Given the WTP threshold of USD 20,000 per QALY gained, pre-screening with QUS followed by DXA for those with a QUS T-score lower than -0.5 and re-screening those with a DXA T-score greater than -2.5 in 2 years had the highest probability (39%) of being the most cost-effective screening strategy across the four non-dominated strategies (*Figure 7.2*). The ICER was USD 11,890 per QALY gained compared with the last effective strategy "QUS (-0.5) + DXA every 5 years". Besides, the incremental cost for an additional fracture averted was USD 5,086 (*Table 7.3*).

Table 7.2. Average costs, effectiveness and incremental cost-effectiveness ratio (ICER) of each screening strategy compared with no screening for women aged 55 years

Strategy	Average lifetime costs (2015 USD)	Average lifetime effectiveness (QALYs)	Lifetime fractures per 1,000 patients			Incremental costs (2015 USD)	Incremental effectiveness (QALYs)	ICER (USD per QALY gained)	ICER(USD per fracture averted)
			Hip	Vertebrae	Wrist				
No screening	1,440	11.024	72	269	174	-	-	-	-
DXA every 2 years	2,185	11.100	45	179	130	746	0.076	9,812	4,632
DXA every 5 years	1,895	11.086	51	199	140	455	0.062	7,341	3,641
DXA every 10 years	1,759	11.067	57	225	153	319	0.043	7,423	3,990
OSTA(-1)+DXA every 2 years	2,009	11.098	47	184	132	569	0.074	7,694	3,746
OSTA(-1)+DXA every 5 years	1,756	11.082	51	201	142	316	0.058	5,449	2,612
OSTA(-1)+DXA every 10 years	1,625	11.058	59	231	157	186	0.034	5,464	2,732
QUS(-0.5)+DXA every 2 years	1,944	11.099	46	180	130	505	0.075	6,691	3,173
QUS(-0.5)+DXA every 5 years	1,761	11.084	51	200	141	321	0.060	5,357	2,613
QUS(-0.5)+DXA every 10 years	1,655	11.062	58	228	155	215	0.038	5,669	2,911
QUS(-1)+DXA every 2 years	2,021	11.099	46	180	131	581	0.075	7,744	3,676
QUS(-1)+DXA every 5 years	1,746	11.085	51	201	140	306	0.061	5,013	2,486
QUS(-1)+DXA every 10 years	1,643	11.059	59	231	157	204	0.035	5,819	2,995

QALY=quality adjusted life year, DXA=dual-energy X-ray absorptiometry, QUS=quantitative ultrasound, OSTA=Osteoporosis Self-Assessment Tool for Asians, USD=United States dollar

Table 7.3. Average costs, effectiveness and incremental cost-effectiveness ratio (ICER) of non-dominated strategies for women aged 55 years

Strategy	Average lifetime costs (2015 USD)	Average lifetime effectiveness (QALYs)	Lifetime fractures per 1,000 patients			Incremental costs (2015 USD)	Incremental effectiveness (QALYs)	ICER (USD per QALY gained)	ICER(USD per fracture averted)
			Hip	Vertebrae	Wrist				
No screening	1,440	11.024	72	269	174	-	-	-	-
QUS(-0.5)+DXA every 5 years	1,761	11.084	51	200	141	321	0.060	5,357	2,613
QUS(-0.5)+DXA every 2 years	1,944	11.099	46	180	130	183	0.015	11,890	5,086
DXA every 2 years	2,185	11.100	45	179	130	241	0.001	402,038	120,612

QALY=quality adjusted life year, DXA=dual-energy X-ray absorptiometry, QUS=quantitative ultrasound, USD=United States dollar

7.5.3 One-way sensitivity analyses

The results of all one-way sensitivity analyses for the base scenario (screening of women 55 years of age) are shown in *Appendix 7B*. Briefly, varying several critical parameter values within the model, generally did not alter the most cost-effective screening strategy, although the ICERs changed slightly. However, if screening sensitivity and specificity were improved by 50%, "QUS (-0.5) + DXA every 5 years" became the most cost-effective strategy. Medication adherence, proportion of full medication costs for poorly adherent women and treatment duration had little impact on ICERs.

Choice of the age at screening initiation had a large impact on the assessment of cost-effectiveness (*Table 7.4*). From age 65 years, all osteoporosis screening strategies dominated no screening giving rise to higher QALYs at lower costs. In a comparison of non-dominated strategies "QUS (-0.5) + DXA every 2 years" remained the most cost-effective screening strategy given the WTP of USD 20,000 per QALY gained.

7.5.4 Cost-effectiveness acceptability curve (CEAC)

The CEAC of all screening strategies is given in *Figure 7.2*. "No screening" has the highest probability (36%) of being cost-effective if the WTP threshold is smaller than USD 7,000 per QALY gained. Given three times per capita GDP in China as the WTP threshold (USD 20,000 per QALY gained), "no screening", "QUS (-0.5) + DXA every 5 years", "QUS (-0.5) + DXA every 2 years" and "DXA every 2 years" had probabilities of being cost-effective of 19%, 37%, 39% and 5% respectively. Given one time per capita GDP as the WTP threshold (USD 6,800 per QALY gained), "no screening", "QUS (-0.5) + DXA every 5 years", "QUS (-0.5) + DXA every 2 years" and "DXA every 2 years" had probabilities of being cost-effective of 37%, 36%, 27% and 0% respectively. Overall, pre-screen with QUS followed by DXA strategies had higher probabilities of being cost-effective compared with DXA alone strategy.

Table 7.4. Average costs, effectiveness of each screening option by 5-year age increments (60-85 years); and incremental cost-effectiveness ratios (ICER) of non-dominated strategies compared with the least effective of those strategies by age

Strategy	Average lifetime costs (2015 USD)	Average lifetime effectiveness (QALYs)	ICER (USD/QALY gained)
Age 60 years			
No screening	1,578	9.776	Baseline
QUS(-0.5)+DXA every 5 years	1,739	9.865	Dominated
QUS(-0.5)+DXA every 2 years	1,633	9.906	421
DXA every 2 years	1,831	9.908	98,900
Age 65 years			
No screening	1,632	8.458	Dominated
QUS(-0.5)+DXA every 5 years	1,570	8.575	Dominated
QUS(-0.5)+DXA every 2 years	1,411	8.613	Baseline
DXA every 2 years	1,586	8.615	87,645
Age 70 years			
No screening	1,700	7.073	Dominated
QUS(-0.5)+DXA every 5 years	1,342	7.218	Dominated
QUS(-0.5)+DXA every 2 years	1,160	7.257	Baseline
DXA every 2 years	1,311	7.259	75,405
Age 75 years			
No screening	1,711	5.710	Dominated
QUS(-0.5)+DXA every 5 years	1,115	5.878	Dominated
QUS(-0.5)+DXA every 2 years	921	5.920	Baseline
DXA every 2 years	1,047	5.922	63,174
Age 80 years			
No screening	1,642	4.441	Dominated
QUS(-0.5)+DXA every 5 years	891	4.630	Dominated
QUS(-0.5)+DXA every 2 years	673	4.675	Baseline
DXA every 2 years	775	4.677	51,160
Age 85 years			
No screening	1,466	3.440	Dominated
QUS(-0.5)+DXA every 5 years	649	3.644	Dominated
QUS(-0.5)+DXA every 2 years	409	3.694	Baseline
DXA every 2 years	494	3.696	42,660

QALY=quality adjusted life year, DXA=dual-energy X-ray absorptiometry, QUS=quantitative ultrasound, OSTA=Osteoporosis Self-Assessment Tool for Asians, USD=United States dollar

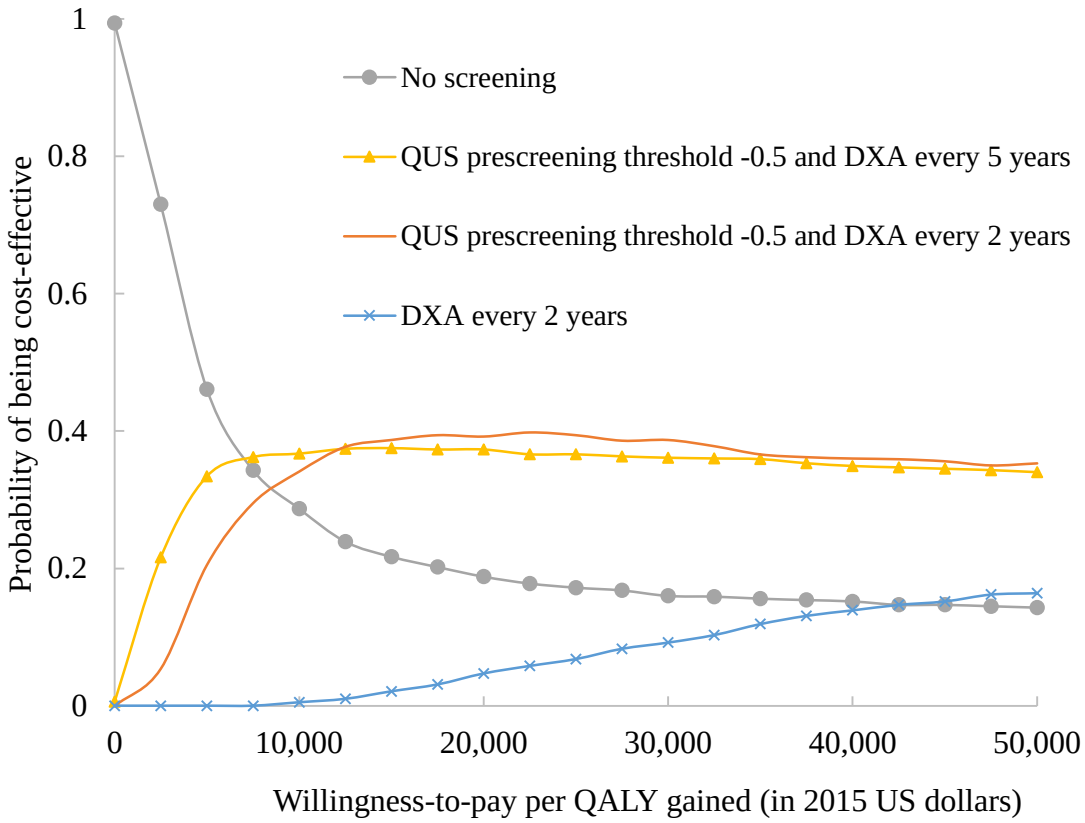

Figure 7.2. Cost-effectiveness acceptability curves of all best screening strategies initiated from age 55 years at different levels of willingness-to-pay (WTP) per quality-adjusted life year (QALY) gained. "No screening" has the highest probability being cost-effective if the WTP threshold is lower than USD 7,000 per QALY gained. Given the WTP threshold of USD 20,000 per QALY gained (3 times per capita Gross Domestic Product, GDP, in China), "no screening", "QUS (-0.5) + DXA every 5 years", "QUS (-0.5) + DXA every 2 years" and "DXA every 2 years" have probabilities of being cost-effective of 19%, 37%, 39% and 5% respectively. Given one time per capita GDP as the WTP threshold (USD 6,800 per QALY gained), "no screening", "QUS (-0.5) + DXA every 5 years", "QUS (-0.5) + DXA every 2 years" and "DXA every 2 years" have probabilities of being cost-effective of 37%, 36%, 27% and 0% respectively.

7.6 Discussion

To our knowledge, this is the first health economics study of the cost-effectiveness of osteoporosis screening strategies in the Chinese setting. In general, all osteoporosis screening strategies are more effective than no screening regardless of screening initiation age in the prevention of fractures. In the direct comparison between an individual screening strategy and no screening in the base-case analysis (screening of women aged 55 years), screening strategies are all cost-effective given the current WTP threshold in China, with "pre-screening with QUS followed by DXA for those with a QUS T-score lower than -0.5 and re-screening those with a DXA T-score greater than -2.5 in 2 years" ascertained as having the highest probability of being the most cost-effective across all screening strategies. Moreover, osteoporosis screening strategies are even cost-saving if the screening initiation age is greater than 65 years.

Screening for osteoporosis has proved cost-effective and has been recommended in many populations [10-12, 44]. However, cost-effectiveness of osteoporosis screenings in Asian populations is still controversial [13, 45]. In postmenopausal Japanese women, it was suggested that DXA screening with hormone replacement therapy (HRT) or alendronate treatment for osteoporotic patients might be cost effective [45]. Only hip fractures were included in that study, therefore effectiveness of screening strategies has been potentially underestimated by the exclusion of other possible fractures [45]. Given the WTP threshold of 100,000 Thai baht (approximately USD 3,000) per QALY gained, it was suggested that osteoporosis screening and treatment strategies were not cost-effective in postmenopausal Thai women [13]. In our analysis, we have also demonstrated different WTP thresholds result in different choices of the most cost-effective screening strategy. When 3 times per capita GDP was used, "QUS (-0.5) + DXA every 2 years" was the most cost-effective strategy with an ICER of USD 11,890 per QALY gained. However, the most cost-effective strategy was altered to "QUS (-0.5) + DXA every 5 years" if one time per capita GDP was used as the WTP threshold. This inconsistency emphasises the importance of conducting country-specific health economic evaluations in osteoporosis screening strategies, given the different characteristics of populations and WTP thresholds in different countries.

Currently there are several guidelines for osteoporosis management in China [7], however, no health economics evidence was used during their development. Our study demonstrated that screening for osteoporosis in postmenopausal Chinese women is cost-effective if the

screening initiation age is 55 years. Moreover, pre-screening with QUS with a subsequent DXA screening for those who were tested positive and re-screening those with a DXA T-score greater than -2.5 in 2 or 5 years dominates no screening if the screening initiation age is 65 years (*Table 7.4*).

Measurement of BMD using DXA scan at the femoral neck is currently the gold standard of diagnosing osteoporosis, however, due to high costs and lack of access, osteoporosis still remains underdiagnosed rather than overdiagnosed in China [17, 46]. QUS and fracture assessment tools such as OSTA are less expensive and easier to use in local clinics to identify women at risk of osteoporosis, therefore they were used as a prescreening strategy in our study. Improvement of accuracy of the prescreening strategy results in identification of more women at risk and less misdiagnoses. In our analysis, we have demonstrated that a total of 35 fractures per 1,000 patients can be averted compared with base case if QUS sensitivity and specificity increased by 50%. Consequently, QALYs for "QUS (-0.5)+DXA every 5 years" have increased by 0.015 compared with base case (*Appendix 7B*).

The recommended time interval between repeated DXA is variable, from 1 year to 15 years based on baseline BMDs [47], however no clear evidence of whether a shorter rescreening interval was superior to a longer time interval was found in previous health economics studies [12]. Our results indicate that in general, shorter a rescreening time interval was associated with higher effectiveness and costs, but was most cost-effective at the 2-year time interval.

Screening initiation age had a high impact on cost-effectiveness. Generally, higher screening initiation ages are associated with lower costs per QALY gained because more osteoporosis patients are identified and treated [11, 12, 44]. Our study confirmed previous findings that screening for osteoporosis is cost-effective from age 55 years, and screenings may be a cost-saving strategy compared with no screening in older postmenopausal women.

Previous studies have indicated that medication persistence and adherence greatly impact the cost-effectiveness of osteoporosis interventions [29, 48]. However, limitations in these previous studies have been identified. Medication persistence and adherence were only accounted for in screening/treatment arms, while no treatment was assumed in no screening arm, even for those who had an osteoporotic fracture [48]. This assumption contradicts several osteoporosis prevention and treatment guidelines, in which treatment is recommended for those with bone density loss and a fragility fracture [49, 50]. In our study, we used the "current practice" as the comparator (no screening) arm [43]. We have addressed previously

identified limitations, as osteoporosis patients who had a fracture in the no screening arm were assumed to receive treatment to prevent following fractures, and the choice of the treatment was based on current osteoporosis treatment patterns in China [19]. Therefore, we incorporated medication persistence and adherence in both no screening and screening arms.

Interestingly, our study also demonstrated that changes in medication persistence and adherence would result in changes in ICERs. Moreover, the changes in ICER were greater for changes in medication persistence compared to adherence. This could be explained by the assumption that no costs of treatment were incurred by the non-persistent patients, and only a 20% cost deduction was applied to non-adherent patients while the changes in effectiveness were minor. Nevertheless, decision of the most cost-effective screening strategies did not alter in one-way sensitivity analyses of medication persistence and adherence (*Appendix 7B*).

There are some limitations to our study. First, we did not include fractures such as humerus, pelvis, ribs and shoulder fractures in this study [16]. This was due to insufficient Chinese epidemiological and economic data on these fractures. Second, the adverse events from treatment were not included in the analysis. Despite that, adverse events from oral alendronate intake, including gastrointestinal tract, osteonecrosis of the jaw, were considered rare at the doses used in the treatment of osteoporosis [51], and thus unlikely to affect the cost-effectiveness of osteoporosis screenings. Third, we have not compared the risks of major fractures calculated from our model to those from FRAX. Because the epidemiological data sources used in our model did not capture all clinical risk factors for osteoporosis, where FRAX has incorporated major clinical risk factors for osteoporosis such as smoking, history of fracture, glucocorticoid use, rheumatoid arthritis and so on. However, we have previously estimated 10-year risks of hip and any major osteoporotic fractures for the Chinese population using our model and compared our results with other populations [5]. Last, some of our model input parameters such as annual wrist fracture rates and osteoporosis attribution rate for annual fracture rates were not available in Chinese population study. Therefore, such inputs were retrieved from studies in other Asian populations [26, 27]. In addition, standardized mortality ratios after fractures, treatment efficacy and HSUV multipliers were not available in the Chinese population, values from Caucasian populations or meta-analysis have been used.

Future research is recommended. First, although bone densitometry was considered as a vital component in the diagnosis and management of osteoporosis, fracture risk assessment tools

that incorporates other clinical risk factors could provide better estimates of absolute fracture risks to inform clinician decision making. FRAX® (http://www.shef.ac.uk/FRAX) has been developed by the WHO and is increasingly used in China, however, concerns have arisen that the intervention threshold for therapeutic interventions was poorly defined in the Chinese population [52]. Future research is encouraged to determine the FRAX intervention threshold for the Chinese population, taking into account both health and economic consequences. Finally, we have identified for healthcare policy makers in China which osteoporosis screening strategy is of best value for money. However, we have not attempted to address issues of affordability (i.e. budget impact) in this analysis, but acknowledge that this would be an area of important future research, given the fact that DXA is not commonly available in China, especially in small-scale cities and rural area.

In conclusion, this study determined the cost-effectiveness of different osteoporosis screening strategies using a validated model in the Chinese setting. Given the WTP threshold of USD 20,000 per QALY gained, pre-screening with QUS followed by DXA for those with a QUS T-score lower than -0.5 and re-screen those with a DXA T-score greater than -2.5 in 2 years, is recommended for Chinese postmenopausal women aged 55 years. If the health payer is not willing to pay extra money for additional effectiveness from the intervention, i.e. with a WTP threshold of USD 0 per QALY gained, screening for osteoporosis from age 65 years is recommended.

7.7 References

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Appendix 7B: One-way sensitivity analyses for all non-dominated strategies

One-way sensitivity analysis for all best screening strategies: 0% discount rates for costs and effectiveness

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	3,918	19.026	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	4,301	19.254	51	200	141	383	0.228	1,678	3,110
QUS(-0.5)+DXA every 2 years	4,551	19.318	46	180	130	250	0.064	3,913	6,956
DXA every 2 years	4,972	19.319	45	179	130	421	0.001	421,087	210,544

One-way sensitivity analysis for all best screening strategies: 8% discount rates for costs and effectiveness

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	911	8.724	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,180	8.757	51	200	141	268	0.033	8,127	2,180
QUS(-0.5)+DXA every 2 years	1,331	8.765	46	180	130	151	0.008	18,898	4,200
DXA every 2 years	1,521	8.766	45	179	130	190	0.000	634,204	95,131

One-way sensitivity analysis for all best screening strategies: 0.5 times QUS sensitivity and specificity

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,440	11.024	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,687	11.080	51	202	143	247	0.056	4,415	2,078
QUS(-0.5)+DXA every 2 years	1,876	11.098	46	181	131	189	0.018	10,476	4,963
DXA every 2 years	2,185	11.100	45	179	130	310	0.002	154,957	77,479

Appendix 7B: One-way sensitivity analyses for all non-dominated strategies

One-way sensitivity analysis for all best screening strategies: 1.5 times QUS sensitivity and specificity

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,440	11.024	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,619	11.099	45	180	132	180	0.075	2,395	1,137
QUS(-0.5)+DXA every 2 years	1,998	11.100	45	179	130	379	0.001	379,002	126,334
DXA every 2 years	2,185	11.100	45	179	130	-	-	Dominated	Dominated

One-way sensitivity analysis for all best screening strategies: 0.8 times base-case annual fracture rates

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,199	11.101	59	222	142	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,556	11.150	42	165	115	357	0.049	7,290	3,537
QUS(-0.5)+DXA every 2 years	1,744	11.161	38	149	107	188	0.011	17,050	6,698
DXA every 2 years	1,984	11.162	38	148	106	240	0.001	240,262	120,131

One-way sensitivity analysis for all best screening strategies: 1.2 times base-case annual fracture rates

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,660	10.950	83	313	205	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,952	11.021	59	233	166	292	0.071	4,115	2,043
QUS(-0.5)+DXA every 2 years	2,129	11.039	52	209	154	177	0.018	9,824	4,113
DXA every 2 years	2,369	11.040	52	208	153	241	0.001	240,504	120,252

One-way sensitivity analysis for all best screening strategies: 0.5 times base-case medication persistence

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,258	11.014	73	276	179	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,475	11.077	51	203	148	216	0.063	3,431	1,715
QUS(-0.5)+DXA every 2 years	1,622	11.092	46	184	139	147	0.015	9,804	4,457
DXA every 2 years	1,855	11.093	46	183	138	234	0.001	233,582	116,791

One-way sensitivity analysis for all best screening strategies: 1.5 times base-case medication persistence

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,614	11.034	69	259	169	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	2,040	11.092	49	196	134	426	0.058	7,342	3,609
QUS(-0.5)+DXA every 2 years	2,261	11.108	44	176	123	221	0.016	13,815	6,140
DXA every 2 years	2,510	11.109	44	175	122	249	0.001	248,786	124,393

One-way sensitivity analysis for all best screening strategies: 0.5 times base-case medication adherence

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,426	11.021	72	272	176	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,735	11.080	52	203	143	310	0.059	5,246	2,537
QUS(-0.5)+DXA every 2 years	1,914	11.095	47	183	133	179	0.015	11,932	5,114
DXA every 2 years	2,155	11.096	47	182	132	241	0.001	240,557	120,279

Appendix 7B: One-way sensitivity analyses for all non-dominated strategies

One-way sensitivity analysis for all best screening strategies: 1.5 times base-case medication adherence

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,455	11.027	71	266	173	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,787	11.088	49	196	138	333	0.061	5,455	2,620
QUS(-0.5)+DXA every 2 years	1,974	11.105	44	176	128	186	0.017	10,965	5,326
DXA every 2 years	2,216	11.106	44	175	127	242	0.001	241,845	120,923

One-way sensitivity analysis for all best screening strategies: no medication offset time effect

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,452	11.019	73	273	196	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,807	11.072	55	214	143	355	0.053	6,700	2,731
QUS(-0.5)+DXA every 2 years	1,997	11.086	50	195	133	190	0.014	13,545	5,578
DXA every 2 years	2,239	11.087	50	194	132	242	0.001	242,076	121,038

One-way sensitivity analysis for all best screening strategies: treatment for 2 years

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,437	11.024	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,674	11.082	21	201	144	237	0.058	4,080	1,588
QUS(-0.5)+DXA every 2 years	1,850	11.097	46	181	133	176	0.015	11,720	29,301
DXA every 2 years	2,089	11.098	45	181	133	239	0.001	239,245	239,245

Appendix 7B: One-way sensitivity analyses for all non-dominated strategies

One-way sensitivity analysis for all best screening strategies: treatment for 10 years

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,440	11.024	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,827	11.087	50	198	138	387	0.063	6,145	3,001
QUS(-0.5)+DXA every 2 years	2,021	11.103	45	178	127	194	0.016	12,104	5,379
DXA every 2 years	2,263	11.104	45	177	127	243	0.001	242,835	242,835

One-way sensitivity analysis for all best screening strategies: 0.5 times base-case annual medication costs

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,227	11.024	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,361	11.084	51	200	141	134	0.060	2,234	1,090
QUS(-0.5)+DXA every 2 years	1,495	11.099	46	180	130	134	0.015	8,919	3,716
DXA every 2 years	1,726	11.100	45	179	130	231	0.001	231,241	115,621

One-way sensitivity analysis for all best screening strategies: 1.5 times base-case annual medication costs

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,652	11.024	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	2,161	11.084	51	200	141	509	0.060	8,480	4,137
QUS(-0.5)+DXA every 2 years	2,394	11.099	46	180	130	232	0.015	15,495	6,456
DXA every 2 years	2,645	11.100	45	179	130	251	0.001	251,204	125,602

One-way sensitivity analysis for all best screening strategies: 50% of full medication costs for poorly adherent women

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,363	11.024	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,680	11.084	51	200	141	317	0.060	5,288	2,580
QUS(-0.5)+DXA every 2 years	1,853	11.099	46	180	130	173	0.015	11,503	4,793
DXA every 2 years	2,092	11.100	45	179	130	239	0.001	239,080	119,540

One-way sensitivity analysis for all best screening strategies: full medication costs for poorly adherent women

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,491	11.024	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,815	11.084	51	200	141	324	0.060	5,403	2,635
QUS(-0.5)+DXA every 2 years	2,005	11.099	46	180	130	190	0.015	12,676	5,282
DXA every 2 years	2,248	11.100	45	179	130	243	0.001	242,652	121,326

One-way sensitivity analysis for all best screening strategies: 0.5 times base-case annual inpatient costs

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	957	11.024	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,361	11.084	51	200	141	404	0.060	6,741	3,288
QUS(-0.5)+DXA every 2 years	1,570	11.099	46	180	130	209	0.015	13,931	5,804
DXA every 2 years	1,813	11.100	45	179	130	243	0.001	242,845	121,423

Appendix 7B: One-way sensitivity analyses for all non-dominated strategies

One-way sensitivity analysis for all best screening strategies: 1.5 times base-case annual inpatient costs

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,923	11.024	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	2,161	11.084	51	200	141	238	0.060	3,973	1,938
QUS(-0.5)+DXA every 2 years	2,318	11.099	46	180	130	157	0.015	10,484	4,368
DXA every 2 years	2,558	11.100	45	179	130	240	0.001	239,601	119,801

One-way sensitivity analysis for all best screening strategies: 0.5 times base-case screening cost

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,440	11.024	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,700	11.084	51	200	141	260	0.060	4,331	2,113
QUS(-0.5)+DXA every 2 years	1,813	11.099	46	180	130	114	0.015	7,587	3,161
DXA every 2 years	1,942	11.100	45	179	130	129	0.001	129,125	64,563

One-way sensitivity analysis for all best screening strategies: 1.5 times base-case screening cost

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,440	11.024	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,823	11.084	51	200	141	383	0.060	6,383	3,114
QUS(-0.5)+DXA every 2 years	2,075	11.099	46	180	130	252	0.015	16,828	7,012
DXA every 2 years	2,428	11.100	45	179	130	353	0.001	353,321	176,661

Appendix 7B: One-way sensitivity analyses for all non-dominated strategies

One-way sensitivity analysis for all best screening strategies: 0.5 times base-case annual nursing home costs

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,416	11.024	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,742	11.084	51	200	141	327	0.060	5,444	2,656
QUS(-0.5)+DXA every 2 years	1,926	11.099	46	180	130	184	0.015	12,289	5,120
DXA every 2 years	2,168	11.100	45	179	130	241	0.001	241,069	120,535

One-way sensitivity analysis for all best screening strategies: 1.5 times base-case annual nursing home costs

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,464	11.024	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,780	11.084	51	200	141	316	0.060	5,270	2,571
QUS(-0.5)+DXA every 2 years	1,962	11.099	46	180	130	182	0.015	12,126	5,052
DXA every 2 years	2,203	11.100	45	179	130	241	0.001	241,377	120,689

One-way sensitivity analysis for all best screening strategies: 0.8 times base-case HSUVs

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,440	8.791	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,761	8.848	51	200	141	321	0.057	5,639	2,613
QUS(-0.5)+DXA every 2 years	1,944	8.861	46	180	130	183	0.013	14,085	5,086
DXA every 2 years	2,185	8.862	45	179	130	241	0.001	241,223	120,612

Appendix 7B: One-way sensitivity analyses for all non-dominated strategies

One-way sensitivity analysis for all best screening strategies: 1.2 times base-case HSUVs

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,440	13.274	72	269	174	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,761	13.333	51	200	141	321	0.059	5,448	2,613
QUS(-0.5)+DXA every 2 years	1,944	13.350	46	180	130	183	0.017	10,771	5,086
DXA every 2 years	2,185	13.351	45	179	130	241	0.001	241,223	120,612

One-way sensitivity analysis for all best screening strategies: 0.8 times treatment efficacy

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,498	11.000	78	291	186	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,828	11.069	54	205	155	329	0.069	4,775	2,337
QUS(-0.5)+DXA every 2 years	2,020	11.081	49	185	145	192	0.012	16,020	5,492
DXA every 2 years	2,263	11.082	49	184	144	243	0.001	243,405	121,703

One-way sensitivity analysis for all best screening strategies: 1.2 times treatment efficacy

Strategy	Lifetime costs	Lifetime effectiveness	Lifetime fractures per 1,000 patients			Incremental costs, 2015 USD	Incremental effectiveness, QALY	ICER, USD per QALY gained	ICER, USD per fracture averted
			Hip	Vertebrae	Wrist				
No screening	1,417	11.033	70	260	170	-	-	Baseline	Baseline
QUS(-0.5)+DXA every 5 years	1,757	11.088	49	192	144	341	0.055	6,191	2,961
QUS(-0.5)+DXA every 2 years	1,941	11.104	44	171	134	184	0.016	11,492	5,108
DXA every 2 years	2,182	11.105	43	171	134	241	0.001	241,203	241,203

QALY=quality adjusted life year, DXA=dual-energy X-ray absorptiometry, QUS=quantitative ultrasound, USD=United States dollar

Chapter 8: Summary and future directions

8.1 Summary of the thesis

In Chapter 1, an introduction to osteoporosis and health economics was provided. Osteoporosis and osteoporotic fractures contribute a substantial and growing disease and economic burden worldwide [1, 2]. What is worse, the general public normally lacks awareness of osteoporosis and its risks [3, 4] and sometimes even the experts provide "*misleading and nihilistic*" recommendations on fracture prevention [5, 6]. Failure to recommend an appropriate prevention strategy to those who are at risk of fracture results in high incidence of fracture events. When recommending a fracture prevention strategy, it should be provided with the clinical and economic merits having been considered. Health economic evaluation is a key means to assist decision makers to ration limited healthcare resource in an attempt to achieve the highest wellbeing at minimal costs. Modelling is an important method in health economic evaluation. It is an "*unavoidable fact of life*" because economic valuations solely based on clinical trials are limited to intermediate endpoints or have short-term follow-up periods [7]. In addition, health economic modelling enables the synthesis of the best available data from different sources. My work on health economic evaluations of osteoporosis interventions was conducted using a modelling approach.

Prior to the development of my own model, a systematic review of previous osteoporosis models was performed and detailed in Chapter 2. The characteristics and evolution of models were summarised and, more importantly, recommendations for the development of future models in this field were provided. A good economic modelling study should follow the well-accepted recommendations [8] and critical appraisals, such as the British Medical Journal (BMJ) checklist [9] and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [10]. A Markov cohort modelling approach was not recommended in osteoporosis due to its memoryless nature [11], because the "memory" of simulated patients such as fracture history is critical to assigning appropriate transition probabilities, utilities and costs in the model. Preferably, a lifetime simulation horizon was recommend to capture all relevant costs and effectiveness. Medication persistence and adherence have huge impacts on cost-effectiveness of osteoporosis interventions, therefore they should be included in the model.

Health state utility values (HSUVs) are used in calculating quality-adjusted life years (QALYs), therefore they are key to cost-effectiveness and cost-utility analysis. For those countries with limited data on HSUVs for osteoporosis-related fractures, data from meta-analysis are preferred. There are two meta-analyses of HSUVs for osteoporosis that were conducted before our study [12, 13], while the HSUVs for conditions after hip and vertebral fractures provided in the later meta-analysis was considerably lower than the previous study. In addition, neither study provided HSUVs for subsequent years after vertebral and wrist fractures due to paucity of data. An updated meta-analysis of HSUVs for osteoporosis-related conditions was conducted; this study was presented in Chapter 3. The pooled HSUVs for pre-fracture, post-hip fracture, post-vertebral fracture and post-wrist fracture were 0.76 (95% CI: 0.75, 0.77), 0.57 (95% CI: 0.52, 0.63), 0.59 (95% CI: 0.55, 0.62), and 0.72 (95% CI: 0.67, 0.78) respectively. Time after fracture contributed to the heterogeneity: HSUVs improved with time after fracture events but remain relatively low compared with those for pre-fracture. In addition, a formula for future modellers to calculate HSUVs in their population of interest has been provided.

With the recommendations for future osteoporosis models from the systematic review and a standard set of HSUVs for osteoporosis-related conditions, a new osteoporosis health economic model has been developed. The construction and validation of the new model was presented in Chapter 4. This new osteoporosis health economic model is a state-transition microsimulation model incorporating major clinical outcomes of osteoporosis. It has been validated in the Chinese population but is flexible to be adapted to other populations. The model was proved to have good face, internal and external validities and can therefore be used with confidence in future economic evaluations of osteoporosis intervention strategies.

Chapters 5-7 presented 3 examples of applications of the osteoporosis health economics model. Disease and economic burden is key to decision makers to understanding the magnitude of the problem incurred by the disease. However, such evidence is lacking in the Chinese population and hence health economic studies are called for by the Chinese guidelines for osteoporosis [14]. Using the osteoporosis health economics model, the lifetime risk of the first osteoporotic fracture in Chinese women and men aged 50 years was estimated to be 40.9% (95% CI: 38.3-44.0%) and 8.2% (95% CI: 6.8-9.3%) respectively. Chinese women were estimated to have similar risks of any osteoporotic fracture compared with the world average. However, the risks of vertebral fracture were higher compared with some other populations such as the Australian, Swedish and Belgian populations. Chinese men were estimated to have lower risks across

different fractures. Approximately 2.33 (95% CI: 2.08, 2.58) million osteoporotic fractures occurred in 2010, costing around USD 9.45 (95% CI: 8.78, 10.11) billion to the Chinese healthcare system. The number and costs of fractures will double by 2035 if no action is taken. These two studies have provided the best evidence of the magnitude of osteoporosis disease and financial burden in China. Moreover, the most cost-effective osteoporosis screening strategy has been identified in an attempt to reduce the impact of osteoporosis. It was found that pre-screening with quantitative ultrasound (QUS) with subsequent dual-energy X-ray absorptiometry (DXA) screening if the QUS T-score≤-0.5 with a 2-year rescreening interval in the Chinese women starting at age 55 is the most cost-effective among 12 screening strategies. Approximately 159 osteoporotic fractures were estimated to be averted per 1,000 people with an additional cost of USD 505, the incremental cost-effectiveness ration (ICER) of the most cost-effective screening strategy is USD 3,137 per QALY gained compared with no screening.

In summary, the model has been thoroughly documented and proven to be valid, and has been successfully used in economic evaluations of fracture prevention.

8.2 Future directions

8.3.1 Collection of country-specific data on costs and HSUVs

Country-specific data on costs and HSUVs related to osteoporosis and osteoporotic fractures is limited to date. Ideally, health economic evaluations should be conducted in country- and population-specific settings using country-specific input data for costs, utilities and probabilities, because using data from other populations reduces the validity and transferability of the health economic evaluation (insert a reference for this). In 2007, the "International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS)" was launched to estimate costs and quality of life related to fractures in 11 countries worldwide [15]. However, no Asian country has been included in the ICUROS. The Asian countries have the largest and most rapidly ageing population, and it has been estimated that half of all the world's hip fractures will occur in Asia by 2050 [16]. As a consequence, Asian countries are in the most need to deal with the disease and financial burden caused by osteoporosis.

Our new osteoporosis health economics model was validated in the Chinese population [17], and numerous application studies were conducted [2, 18]. The limitation was acknowledged that some data inputs in our model, such as HSUV multipliers, were based on other populations due to the paucity of such data in the Chinese population. Based on preliminary work in this field, I have received a grant funded by the National Natural Science Foundation of China (CIA, Grant number: 71503007) to collect costs and HSUV data in the Chinese population and this study has been included in the ICUROS study as the Chinese arm. This study will

contribute greatly to the current literature in this field and improve the validity of our model in its use in the Chinese population.

8.3.2 Cost-effectiveness of osteoporosis treatments for the Chinese population

Calcium and vitamin D supplements, calcitonin, raloxifene, alphacalcidol, alendronate and zoledronic acid are listed as first-line osteoporosis drugs in China and they are fully or partly reimbursed by social health insurance [19]. However, economic evidence to support the drug reimbursement policy in China has been lacking to date and no study has been conducted to systematically evaluate the cost-effectiveness of these first-line drugs. For example, alphacalcidol, calcitonin and raloxifene was found to be not cost-effective to treat established osteoporosis but they are still reimbursed as first-line drugs in China [20]. By contrast, there are some drugs which were proven to be cost-effective in the Caucasian population, however, they are not reimbursed in the Chinese population. For example, denosumab is a novel agent for the treatment of osteoporosis in postmenopausal women with increased risk of fractures and it is generally cost-effective compared with other first- and second-line osteoporosis drugs [21]. However, no economic evaluation of denosumab has been conducted in the Chinese population and it is still not reimbursed in China.

An economic evaluation study of all osteoporosis medications that are currently available in the Chinese market will be conducted to identify those that represent good value for money in the Chinese population. This study will assist policy makers to update the essential drug list in osteoporosis as well as to provide clinicians with economic evidence to underpin their clinical practice.

8.3.3 Determination of intervention thresholds for fracture risk assessment tools

It is well acknowledged that fracture risk assessment is not solely based on bone mineral densities (BMDs), but other clinical risk factors. Several fracture risk assessment tools have been developed incorporating clinical risks factors with or without BMD, such as FRAX (http://www.shef.ac.uk/FRAX/) and the Garvan Bone Fracture Risk Calculator (http://www.garvan.org.au/bone-fracture-risk). Clinicians make treatment decisions based on absolute risks of future fractures, such as 5- or 10-year fracture risks, generated from these risk assessment tools. For example, in the United States a patient with low BMD is recommended to be treated when the 10-year probability of any major osteoporotic fracture is 20% or above or when the 10-year hip fracture risks exceeds 3% [22]. These intervention thresholds may only be relevant to the US population and the generalisability to other populations should remain be determined because of different fracture risks in different populations with varying levels of socioeconomic development, treatment patterns and other health economic consideration.

However, they have been used in osteoporosis guidelines in other countries including China without justification [14, 23]. Future study is encouraged to define the treatment thresholds for the Chinese taking into consideration both health and economic consequences in this specific population.

8.3.4 Patients' preference in osteoporosis treatments

Numerous studies have shown medication adherence and persistence impact on costs, effectiveness and cost-effectiveness of therapeutic interventions [24-26]. Medication efficacy is reduced by poor adherence and persistence, therefore improvement in medication adherence and persistence is another important issue to be addressed in the real world setting. Understanding patients' preferences for different treatments is important to improve medication adherence and persistence. A Belgian study found that osteoporotic patients preferred 6-month subcutaneous injection and oral monthly tablets compared with weekly oral tables, 3-month subcutaneous injections, 3 month and yearly intravenous injections [27]. The evidence of patients' preferences for osteoporosis treatments is still limited in most other countries. Given differences in medication patterns, out-of-pocket payments, socioeconomic status and preference for medication administration route, future studies investigating patients' preference for osteoporosis drugs are encouraged in other countries including China.

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Publications of the thesis

Chapter 2:

Si L, Winzenberg TM, Palmer AJ. A systematic review of models used in cost-effectiveness analyses of preventing osteoporotic fractures. *Osteoporosis International*, Jan 2014; 25(1): 50-60.

Chapter 3:

Si L, Winzenberg TM, de Graaff B and Palmer A.J., A systematic review and meta-analysis of utility-based quality of life for osteoporosis-related conditions. *Osteoporosis International*, Aug 2014, 25(8): 1987-97.

Chapter 4:

Si L, Winzenberg TM, Jiang Q, Palmer AJ. Screening for and treatment of osteoporosis: construction and validation of a state-transition microsimulation cost-effectiveness model. *Osteoporosis international*, May 2015. 26(5): 1477-89.

Chapter 5:

Si L, Winzenberg TM, Chen M, Jiang Q, Palmer AJ. Residual lifetime and 10-year absolute risks of osteoporotic fractures in Chinese men and women. *Current Medical Research & Opinion*, June 2015. 31(6):1149-56.

Chapter 6:

Si L, Winzenberg TM, Jiang Q, Chen M, Palmer AJ. Projection of Osteoporosis-Related Fractures and Costs in China: 2010-2050. *Osteoporosis International*, July 2015. 26(7): 1929-37.

Chapter 7:

Si L, Winzenberg TM, Chen M, Jiang Q, Neil A, Palmer AJ. Screening for Osteoporosis in Chinese Post-Menopausal Women: a Health Economic Modelling Study. *Osteoporosis International* 2016. Doi: 10.1007/s00198-016-3502-1

Conference presentations of the thesis

Oral presentations

2013 The 4th Australia-China Biomedical Research Conference & 2013 International Symposium on Aging Biology and Diseases; Hangzhou CHINA.

"*A Systematic Review and Meta-Analysis of Utility-Based Quality of Life in Asian Osteoporosis Related Vertebral Fracture Patients*" 10-13 October

2014 The 2nd Australian Health Economics Doctoral (AHED) Workshop & The 36th Annual Australian Health Economics Society (AHES) Conference. Adelaide, AUSTRALIA.

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2014 International Osteoporosis Foundation Regionals: The 5th Asia-Pacific Osteoporosis Meeting, Taipei, CHINA.

"*Projection of Incidence and Economic Burden of Osteoporosis-related Fractures in China: 2010-2050*" 14-16 November

2015 World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, Milan, ITALY.

"*Ten-year risks of first osteoporotic fractures in Chinese women and men*" 26-29 March

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"*Construction, validation and applications of an osteoporosis health economics model*" 28 May

2015 2015 Emerging Health Policy Research Conference, Sydney, AUSTRALIA.

"*Universal screening for osteoporosis in Chinese post-menopausal women?*" 21 July

Poster presentations

2014 ISPOR (International Society for Pharmacoeconomics and Outcomes Research) 6th Asia Pacific Conference. Beijing, CHINA.

"*Cost-effectiveness analyses of screening and treatment strategies for postmenopausal osteoporosis in Chinese women*" 6-9 September

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"*Residual lifetime risks of first osteoporotic fractures in Chinese women and men*" 26-29 March

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2013.07 Travel grant for Australia Chinese Association for Biomedical Science (ACABS) Five Minutes Competition, Melbourne, Australia

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Grants received related to the work described in this thesis

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2015.05 ASMR (Australian Society for Medical Research) Medical Research Week Tasmanian Postgraduate Student Research Award (Winner). Hobart, Australia

2015.03 ESCEO-Eli Lilly 2015 Scholarship. The World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, Milan, Italy.

2015.02 "Chinese Government Award For Outstanding Self-Financed Students Abroad". Ministry of Education, China.

2014.11 International Osteoporosis Foundation (IOF) Young Investigator Award. The 5th Asia-Pacific Osteoporosis Meeting, Taipei

2014.09 AHES Student Scholarship, The 36th Annual Australian Health Economics Society (AHES) Conference. Adelaide, Australia

2014.09 2014 Student Travel Grant, The ISPOR (International Society for Pharmacoeconomics and Outcomes Research) 6th Asia-Pacific Conference, Beijing, China

2014.09	Best Poster Research Presentation (2nd author), The ISPOR (International Society for Pharmacoeconomics and Outcomes Research) 6th Asia-Pacific Conference, Beijing, China
2013.10	Travel grant, The 4th Australia-China Biomedical Research Conference & 2013 International Symposium on aging biology and diseases. Hangzhou, China
2013.07	Travel grant for Australia Chinese Association for Biomedical Science (ACABS) Five Minutes Competition, Melbourne, Australia
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GRANTS

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2016.01-2018.12	**Chief Investigator C:** Study on Strategy Construction of Health Care Financing Mechanism for Universal Health Coverage: the Perspective of Redistributive Effect of Health Finance, National Natural Science Foundation of China (grant number: 71503137), 230,000 RMB
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RESEARCH EXPERIENCE

2015. 02-	Improving care through embedding general practitioners within

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2009.01 – 2011.12	Benefit Incidence Analysis (BIA) on New Cooperative Medical Scheme (National Natural Science Foundation of China), Data collection and analysis
2008 – 2009	Evaluation of a pilot CMS in rural China (International Scientific Project with University of Alberta, Canada), Data collection
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PUBLICATIONS

Publication summary: Total publications: n= 24, First/Last author publications: n=14.

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Healthcare Subsidies? An Assessment of the Equity of Healthcare Benefits Distribution in China. *PloS one*. 2015 Mar 17;10(3):e0119840. doi: 10.1371/journal.pone.0119840.

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1. Si, Lei. Pharmacoeconomics [in Chinese]. In Qicheng Jiang ed. Health Economics. Beijing: People's Medical Publishing House. (coming soon)
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CONFERENCE ABSTRACTS （PRESENTING AUTHOR）

1. **Oral** presentation: 2015 Emerging Health Policy Research Conference, Sydney, Australia

   Si, L, T.M. Winzenberg, and A.J. Palmer, Universal screening for osteoporosis in Chinese post-menopausal women?

2. **Oral** presentation: ASMR (Australian Society for Medical Research) Medical Research Week, Hobart, Australia

   Si, L, T.M. Winzenberg, and A.J. Palmer, Construction, validation and applications of an osteoporosis health economics model

3. **Oral** presentation: World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, Milan, Italy.

   Si, L, T.M. Winzenberg, and A.J. Palmer, Ten-year risks of first osteoporotic fractures in Chinese women and men.

4. **Poster** presentation: World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, Milan, Italy.

   Si, L, T.M. Winzenberg, and A.J. Palmer, Residual lifetime risks of first osteoporotic fractures in Chinese women and men.

5. **Oral** presentation: International Osteoporosis Foundation Regionals: The 5th Asia-Pacific Osteoporosis Meeting, Taipei, China.

   Si, L, T.M. Winzenberg, Q Jiang, M. Chen, A.J. Palmer, Projection of Incidence and Economic Burden of Osteoporosis-related Fractures in China: 2010-2050.

6. **Oral** presentation: The 36th Annual Australian Health Economics Society (AHES) Conference. Adelaide, Australia

   Si, L., T.M. Winzenberg, Q. Jiang, A.J. Palmer, Construction and Validation of a State-transition Microsimulation Cost-effectiveness Model of Screening for and Treatment of Osteoporosis

7. **Oral** presentation: The 2nd Australian Health Economics Doctoral (AHED) Workshop. Adelaide, Australia

   Si, L., T.M. Winzenberg, Q. Jiang, A.J. Palmer, Construction and Validation of a State-transition Microsimulation Cost-effectiveness Model of Screening for and Treatment of Osteoporosis

8. **Poster** presentation: ISPOR (International Society for Pharmacoeconomics and Outcomes Research) 6th Asia Pacific Conference. Beijing, China

   Si, L., T.M. Winzenberg, L. Wang, A.J. Palmer, Cost-effectiveness analyses of screening and treatment strategies for postmenopausal osteoporosis in Chinese women

9. **Oral** presentation: The 4th Australia-China Biomedical Research Conference & 2013 International Symposium on aging biology and diseases. Hangzhou, China

   Si, L., T.M. Winzenberg, and A.J. Palmer, A Systematic Review and Meta-Analysis of Utility-Based Quality of Life in Asian Osteoporosis Related Vertebral Fracture Patients. *Clinical and Experimental Pharmacology and Physiology* (2013) 40 (Suppl. 1)

TEACHING EXPERIENCE

1. Practical Methods for Health Economic Evaluation, 26-28 Nov. 2014 Hobart, Australia
2. Practical Methods for Health Economic Evaluation, 10-14 Sept. 2014 Hefei, China

LEADERSHIP, MANAGEMENT AND ADMINISTRATION

2014.06 - Committee member on the International Diabetes Federation (IDF) Task Force on Health Economics

2013.04 - Vice Chairman of Australian Chinese Association of Biomedical Science, Tasmania branch

JOURNAL POSITIONS

2015.04 – 2017.10 Youth Editor, Chinese Journal of Osteoporosis

REFEREEING ACTIVITIES

Journals

Annals of Internal Medicine (co-reviewer), Osteoporosis International, Diabetic Medicine, Journal of Clinical Endocrinology & Metabolism, Yonsei Medical Journal, Chinese Medical Journal, Journal of Pain Research

Conference review committees

ISPOR 6th Asia-Pacific Conference

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